Specification

Aminopyrimidine derivative and applications thereof as a drug.

The Field of Technology

(0001)

This invention relates to novel aminopyrimidine compound, and to drug containing this as an active ingredient.

Background Technique

(0002)

Protein kinases are known to participate in signal transduction which controls activation, growth and differentiation of cells in response to extracellular mediators and change of environment. Protein kinases in general are classified into two groups according to their phosphorylation substrate: serine / threonine kinases and tyrosine kinases.

(0003)

It is known that abnormal activation of protein kinases causes many diseases which are accompanied by abnormal cell proliferation. For example, excessive proliferation disorder such as cancer, tumor, hyperplasia, pulmonary fibrosis, angiogenesis, psoriasis, atheroma, stenosis or restenosis after angioplasty and vascular smooth muscle proliferation may be proposed.

(0004)

Wherein, malignant tumor is produced as a result of cancerous cells caused by the failure of cell control through multi-stage gene change. A typical cancer cell has acquired an abnormally high growth capacity, in addition to the ability to invade the surrounding tissue and the ability to move to different organ sites. The defect of normal control of cell proliferation is thought to be generated by abnormality of the signal transduction system which controls the progress of the cell cycle.

(0005)

In eukaryotes, the cell cycle is mainly controlled by signal transduction pathway of protein phosphorylation, and some protein kinases have been identified as being involved in this control.

(0006)

As one of these protein kinases, aurora kinase may be proposed. Aurora kinase family is the protein family in which at least three kinds are related at present. Aurora kinase is highly conserved serine / threonine kinase, and is regarded as important enzyme in the progression of the M phase since it is is expressed in the M phase of the cell cycle. The importance of this kinase family in M phase was suggested from a function inhibition experiment of aurora 2 kinase homologous gene using yeast

and Drosophila, nematode (Non-Patent Literature 1 and Non-Patent Literature 2). Moreover the fact that aurora 2 kinase is over-expressed in many cancers (Non-Patent Literature 3, Non-Patent Literature 4, Non-Patent Literature 5, Non-Patent Literature 6 and Non-Patent Literature 7) and the fact that in experimentally normal cells, the cells show signs of becoming malignant when aurora 2 kinase is over-expressed have become clear.

(0007)

Moreover, when expression of aurora 2 kinase was inhibited by treating human tumor cell system with antisense oligonucleotide, it was shown that cell proliferation was inhibited (Patent Citation 1). From this, it is thought that it should be possible to inhibit cell neoplasia by inhibiting the activity of aurora 2 kinase, which would be useful in therapy of many diseases which are accompanied by cell neoplasia, including cancer.

(0008)

There have been various reports of low molecules which inhibit aurora 2 kinase. For example, Patent Citation 2, Patent Citation 3, Patent Citation 4, Patent Citation 5 and Non-Patent Literature 9 may be proposed.

(0009)

Moreover there are reports of aminopyridine compounds having thiazole ring at 4 position in the following patents. For example, Patent Citation 6, Patent Citation 7, Patent Citation 8, Patent Citation 9, Patent Citation 10 and Non-Patent Literature 10 may be proposed, but there is no report relating to aurora 2 kinase inhibiting activity in these.

Patent Citation 1 : Kokai 2002-95479,
Patent Citation 2 : WO2001-21595,
Patent Citation 3 : WO2002-22601,
Patent Citation 4 : WO2002-96905,
Patent Citation 5 : WO2004-5283,
Patent Citation 6 : WO1997-19065,
Patent Citation 7 : WO2001-72745,
Patent Citation 8 : WO2002-46170,
Patent Citation 9 : WO2003-11838,
Patent Citation 10 : WO2003-29249,
Non-Patent Literature 1: David M. Glover et al, Cell, 81, 95-105, 1995,
Non-Patent Literature 2: Daniela Berdnik et al, Current Biology, 12, 640-647, 2002,
Non-Patent Literature 3: Hongyi Zhou et al, NatureGenetics, 20, 189-193 1998,
Non-Patent Literature 4: Takuji Tanaka et al, Cancer Research, 59, 2041-2044 1999,

Non-Patent Literature 5: C.Sakakura et al, British Journal of Cancer, 84, 824-831 2001,
Non-Patent Literature 6: Subrata Sen et al, Journal of the National Cancer Institute, 94, 1320-1329 2002,
Non-Patent Literature 7: Donghui Li et al, Clinical Cancer Research, 9, 991-997 2003,
Non-Patent Literature 8: James R.Bischoff et al, EMBO Journal, 17, 3052-3065 1998,
Non-Patent Literature 9: Elizabeth A. Harrington et al, Nature Medicine Advanced Online Publication, 2004 February 22,
Non-Patent Literature 10: Shudong Wang et al, Jounal of Medicinal Chemistry, 47 1662-1675 2004.

Disclosure of the Invention

Problems to be Overcome by this Invention.

(0010)

Although there are reports of some substances inhibiting aurora 2 kinase, none having sufficient biological activity in therapy of disease has yet been found. The object of this invention is to put forward aurora 2 kinase inhibitor useful for therapy of cell proliferating disease including cancer.

Means to Overcome these Problems

(0011)

This invention results from carrying out assiduous investigations looking at such a situation and the discovery that aminopyrimidine compounds represented by following general formula (1) and medicinally permissible salt, hydrate, aqueous adduct and solvate strongly inhibited protein kinase, in particular aurora 2 kinase, and is a compound which can act satisfactorily in vivo. This invention was completed on the basis of this discovery.

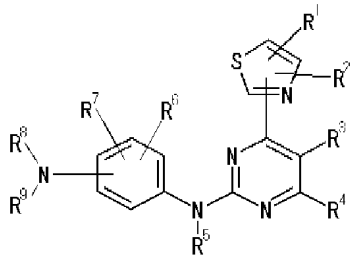
(0012)

In other words, a summary of this invention is as follows.

(1) A compound represented by formula

(0013)

.**[0014]**



(I)

[wherein, R1 and R2 are the same or different, and denote halogen atom, alkyl, hydroxy, alkoxy, amino, alkylamino or acylamino,
R3 and R4 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy or alkoxy,
R5 denotes a hydrogen atom, alkyl or acyl,
R6 and R7 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy, alkoxy, amino, alkylamino, acylamino, carbamoyl, alkylcarbamoyl, carboxy, alkoxycarbonyl, sulphamoyl, alkyl sulphamoyl, nitro or cyano,
R8 denotes COR10, CO2R10, CONR10R11, CSNR10R11, SO2R10 or OR10 [wherein, R10 and R11 are the same or different and denote -T-R12 {wherein, T may be absent or denotes 1-6C alkylene, 2-6C alkenylene, 2-6C alkynylene or one in which 1-3 methylenes in said alkylene, alkenylene, alkynylene have been replaced by C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)N(R14)-, -OC(=O)N(R14)-, -NR14-, -N(R14)O-, N(R14)C(=O)-, -N(R14)C(=O)O-, -N(R14)C(=O)N(R15)-, -S(O2)-, NR14S(O2)-, -S(O2)N(R14)-, -N(R14)C(NH)N(R15)-, oxygen atom or sulfur atom (wherein, R14 and R15 are the same or different, and denote hydrogen or alkyl), R12 denotes hydrogen, halogen atom, hydroxy, alkyl, amino, cycloalkyl, heterocycle or aryl)}, or R10 and R11 together with the nitrogen to which they are bonded denotes group forming 5-7 membered ring],
R9 denotes a hydrogen atom, alkyl, hydroxy, alkoxy or acyl, and when R8 denotes OR10, then R9 denotes a hydrogen atom;
or R8 and R9 together with the nitrogen atom to which they are bonded denote group forming 5-7 membered ring].
and medicinally permissible salt, hydrate, aqueous adduct or solvate.

(2) A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with the aforesaid (1), wherein in the aforesaid formula (1)
R3 and R4 may be the same or different and denote a hydrogen atom or alkyl,
R6 and R7 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy or alkoxy,
R8 denotes COR10, CONR10R11, SO2R10 or OR10 (wherein, R10 and R11 are the same or different and denote -T-R12 {wherein, T may be absent or denotes 1-6C alkylene or the said alkylene wherein 1-3 methylenes have been replaced by C(=O)-, -C(=O)O-, -C(=O)N(R14)-, --NR14-, N(R14)C(=O)-, or oxygen atom}, or R10 and R11 together with the nitrogen to which they are bonded denotes group forming optionally substituted 5-7 membered ring which may further include heteroatom selected from oxygen atom, sulfur atom and NH},
R9 denotes a hydrogen atom, alky, or acyl,
or R8 and R9 together with the nitrogen atom to which they are bonded denote group forming 5-7 membered ring.

(3) A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with the aforesaid (1) or (2) wherein R1 and R2 in the aforesaid formula (1) are the same or different, and denote alkyl or acylamino.

(4) A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of the aforesaid (1)-(3) wherein R3 and R4 in the aforesaid formula (1) respectively denote hydrogen atoms.

(5) Compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of the aforesaid (1)-(3) wherein R5 in the aforesaid formula (1) denotes a hydrogen atom.

(6) A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of the aforesaid (1)-(5) wherein R3 and R4 in the aforesaid formula (1) respectively denote hydrogen atoms, and R5 denotes a hydrogen atom.

(7) Treatment and/or prevention agent of cancer characterised by containing aminopyrimidine compound represented by the aforesaid (1)-(6) or medicinally permissible salt, hydrate, aqueous adduct and solvate therof.

Advantages Afforded by this Invention

(0015)

In accordance with this invention, it is possible to put forward cancer therapeutic drug including, as an active ingredient, A substance selected from the group comprising aminopyrimidine compound represented by the aforesaid general formula (1), medicinally permissible salt, hydrate, hydrate and solvate.

Ideal form for Carrying Out the Invention

(0016)

Hereinafter, this invention will be described in greater detail.

(0017)

Below each substituent represented by the aforesaid general formula (1) of this invention is defined.

(0018)

As "halogen atom" represented by R1 or R2, for example fluorine atom, chlorine atom, bromine atom, iodine atom and the like may be proposed.

(0019)

As "alkyl" represented by R1 or R2, alkyl of 1-6C (for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl and the like) may be proposed, 1-3C alkyl (for example methyl, ethyl, propyl, isopropyl) is preferred, and methyl in particular is preferred.

(0020)

As "alkoxy" represented by R1 or R2, for example alkoxy of 1-6C may be proposed and specifically methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and the like may be proposed, and preferably methoxy may be proposed.

[0021]

As "alkylamino" represented by R1 or R2, for example alkylamino of 1-6C may be proposed and specifically methylamino, ethylamino, n-propylamino, isopropyl-amino, n-butylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, pyrrolidin-1-yl, piperidin-1-yl are proposed, preferably methylamino, dimethylamino may be proposed.

[0022]

As "acylamino" represented by R1 or R2, for example acylamino of 1-6C may be proposed and specifically formylamino, acetylamino, propionyl amino, butyryl amino may be proposed, and preferably acetylamino may be proposed.

[0023]

Alkyl, alkoxy, alkylamino or acylamino represented by R1 or R2, may have a substituent. Wherein, as the substituent, for example alkyl of 1-6C (for example, methyl, ethyl and the like), halogen atom (for example fluorine atom, chlorine atom, bromine atom, iodine atom or the like), hydroxy, 1-6C alkoxy, oxo, carboxy, alkoxycarbonyl of 1-6C (for example tert-butoxycarbonyl and the like), acyl (for example, formyl and the like), acyl oxy, amino, alkylamino, dialkylamino, amido, alkyl amido, carbamoyl, sulphanyl, alkyl sulphanyl, sulfino, alkylsulfonyl (for example, methylsulfonyl, ethylsulfonyl and the like), sulphamoyl, alkyl sulphamoyl and the like may be proposed.

[0024]

As "halogen atom" represented by R3 or R4, the same ones may be proposed as "halogen atom" represented by the aforesaid R1 or R2.

[0025]

As "alkyl" represented by R3 or R4, same ones as in "alkyl" represented by the aforesaid R1 or R2 may be proposed, and preferably methyl may be proposed.

[0026]

As "alkoxy" represented by R3 or R4, the same ones may be proposed as "alkoxy" represented by the aforesaid R1 or R2.

[0027]

Alkyl or alkoxy represented by R3 or R4 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0028]

As "alkyl" represented by R5, same one as in "alkyl" represented by the aforesaid R1 or R2 may be proposed, and preferably carbinyl may be proposed.

[0029]

As "acyl" represented by R5, for example acyl of 1-6C is nominated, specifically formyl, acetyl, propionyl, 2-methyl propionyl, butyryl and the like may be proposed, and preferably acetyl may be proposed.

[0030]

Alkyl or acyl represented by R5 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0031]

As "halogen atom" represented by R6 and R7, same one as in "halogen atom" represented by the aforesaid R1 or R2 may be proposed, and preferably chlorine atom may be proposed.

[0032]

As "alkyl" represented by R6 and R7, same one as in "alkyl" represented by the aforesaid R1 or R2 may be proposed, and preferably methyl may be proposed.

[0033]

As "alkoxy" represented by R6 and R7, same one as in "alkoxy" represented by the aforesaid R1 or R2 may be proposed, and preferably methoxy may be proposed.

[0034]

As "alkylamino" represented by R6 and R7, same one as in "alkylamino" represented by the aforesaid R1 or R2 may be proposed, and preferably methylamino, dimethylamino may be proposed.

[0035]

As "acylamino" represented by R6 and R7, same ones as "acylamino" represented by the aforesaid R1 or R2 may be proposed.

[0036]

As "alkylcarbamoyl" represented by R6 and R7, for example alkylcarbamoyl of 1-6C may be proposed and specifically methylcarbamoyl, ethyl carbamoyl, dimethylcarbamoyl, ethylmethyl carbamoyl and the like may be proposed.

[0037]

As "alkoxycarbonyl" represented by R6 and R7, for example alkoxycarbonyl of 1-6C may be proposed and specifically methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, isopropoxy carbonyl, butoxycarbonyl, t-butoxy carbonyl and the like may be proposed.

[0038]

As "alkyl sulphamoyl" represented by R6 and R7, for example alkyl sulphamoyl of 1-6C may be proposed and specifically methyl sulphamoyl, ethyl sulphamoyl and the like may be proposed.

[0039]

Alkyl, alkoxy, alkylamino, acylamino, alkylcarbamoyl, alkoxycarbonyl or alkyl sulfamoyl represented by R6 or R7 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0040]

As "alkyl" represented by R9, same one as in "alkyl" represented by the aforesaid R1 or R2 may be proposed, and preferably methyl may be proposed.

[0041]

As "alkoxy" represented by R9, the same ones may be proposed as "alkoxy" represented by the aforesaid R1 or R2.

[0042]

As "acyl" represented by R9, same one as in "acyl" represented by the aforesaid R4 may be proposed, and preferably acetyl, butyryl and benzoyl may be proposed.

[0043]

Alkyl, alkoxy or acyl represented by R9 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0044]

As for the group wherein R8 and R9 together with nitrogen atom to which they are bonded form a 5-7 membered ring, a heteroatom selected from the oxygen atom, sulfur atom and N-R13 (R13 denotes a hydrogen atom, alkyl, aralkyl or acyl) may be included in the 5-7 membered ring. As 5-7 membered ring, for example, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, thiazole, isoxazole may be proposed. Moreover, 5-7 membered-ring may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed, and in addition, oxygen atom and the like may be proposed.

[0045]

As for the group wherein R10 and R11 together with nitrogen atom to which they are bonded form a 5-7 membered ring, a heteroatom selected from the oxygen atom, sulfur atom and nitrogen atom may be included in the 5-7 membered ring. As 5-7 membered ring, for example, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, thiazole, isoxazole may be proposed. Moreover, 5-7 membered-ring may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0046]

As "alkyl" represented by R12, same one as in "alkyl" represented by the aforesaid R1 or R2 is proposed, but preferably alkyl of 1-4C is proposed, specifically example methyl, ethyl, isopropyl, tert-butyl, trifluoroethyl may be proposed.

[0047]

As "halogen atom" represented by R12, same one as in "halogen atom" represented by the aforesaid R1 or R2 may be proposed, and preferably chlorine atom and bromine atom may be proposed.

[0048]

As "cycloalkyl" represented by R12, for example cycloalkyl of 3-8C may be proposed and specifically cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like may be proposed, and preferably cyclopropyl, cyclohexyl may be proposed.

[0049]

As "heterocycle" represented by R12, for example, 5 to 7 membered heteroaromatic ring or non heteroaromatic ring that contains 1-4 heteroatoms of 1 or 2 species selected from oxygen atom, sulphur atom and nitrogen atom in addition to carbon atoms may be proposed, specifically pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, thiophene, furan, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, thiazole, isoxazole are proposed, preferably piperazine, piperidine, morpholine, homo piperazine, thiophene, pyridine, thiazole may be proposed.

[0050]

As "aryl" represented by R12, monocycle or condensed ring may be proposed, for example phenyl, 1-naphthyl, 2-naphthyl and the like may be proposed, and preferably phenyl may be proposed.

[0051]

Alkyl, amino, cycloalkyl, heterocycle or aryl represented by R12 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed, in addition heterocyclic (for example 4-methyl piperazino methyl, morpholinomethyl and the like) may also be proposed.

[0052]

As "alkyl" represented by R13, the same ones may be proposed as "alkyl" represented by the aforesaid R1 or R2 may be proposed.

[0053]

As "aralkyl" represented by R13, for example aralkyl of 7-16C may be proposed and for example benzyl, phenethyl, diphenylmethyl, 1-naphthylmethyl and the like may be proposed.

[0054]

As "acyl" represented by R13, the same ones may be proposed as "acyl" represented by the aforesaid R4

[0055]

Alkyl, aralkyl or acyl represented by R13 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

[0056]

As "alkyl" represented by R14 and R15, the same ones may be proposed as "alkyl" represented by the aforesaid R1 or R2.

[0057]

Alkyl represented by R14 and R15 may have a substituent. Wherein as substituent, same group as substituent represented by the aforesaid R1 or R2 may be proposed.

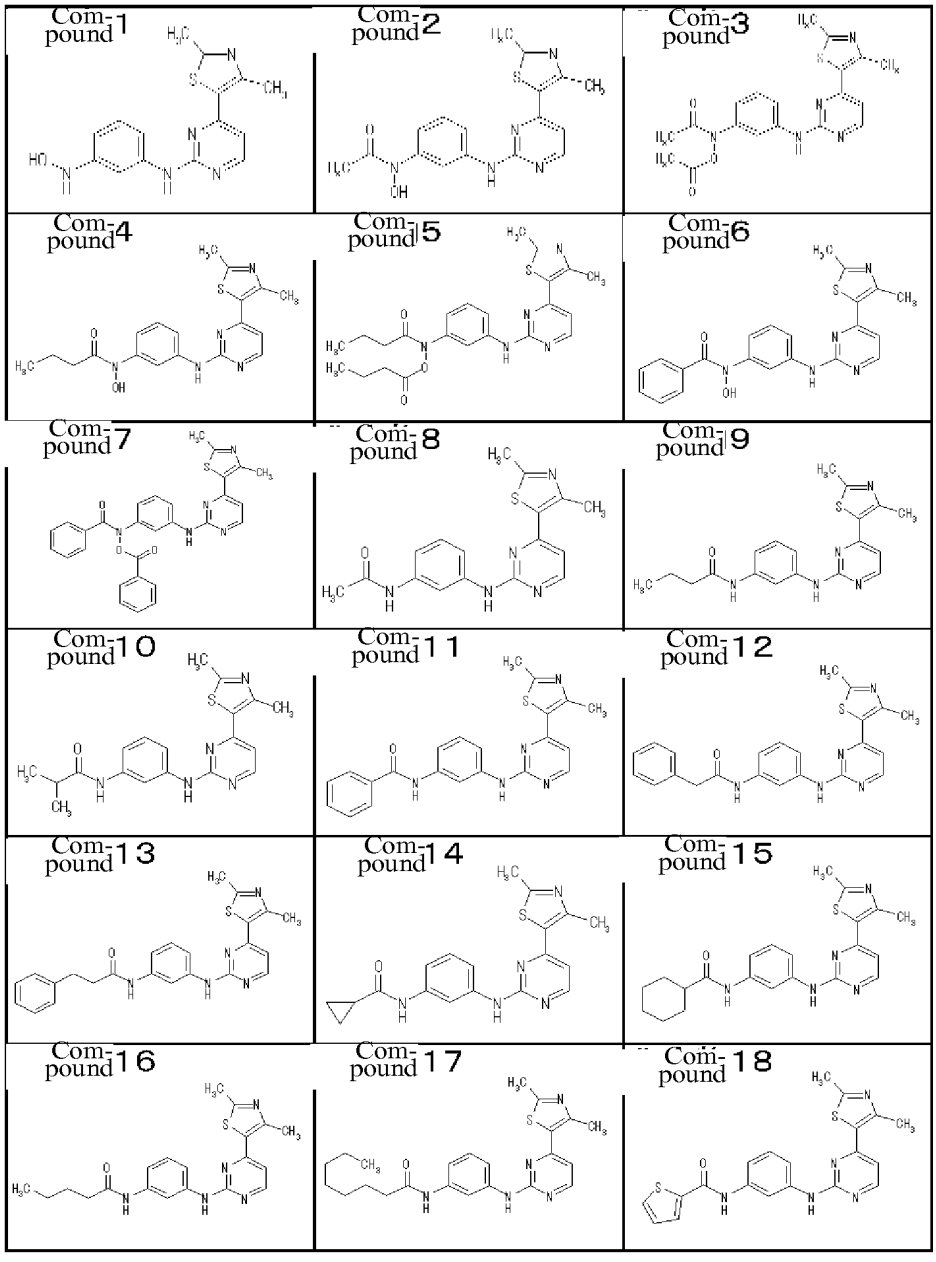
(0058)

As embodiment of the compounds of this invention, for example the following compound may be proposed.

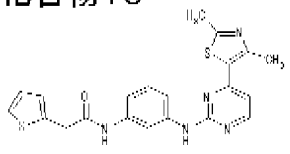
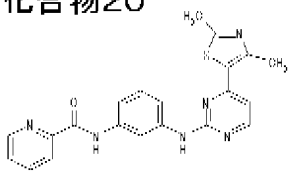
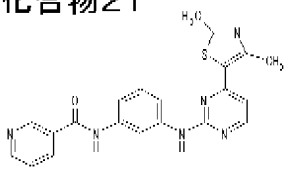
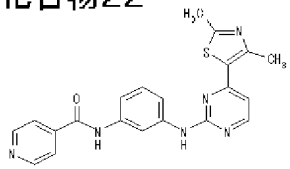
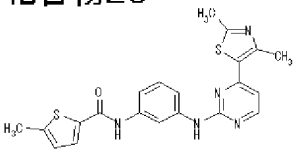
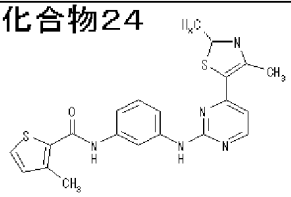
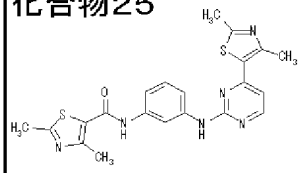
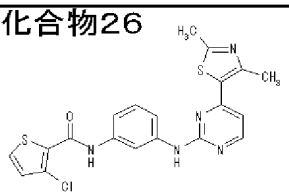
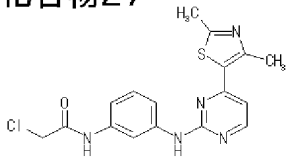
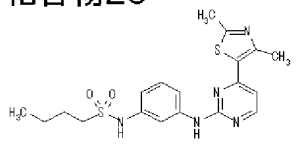
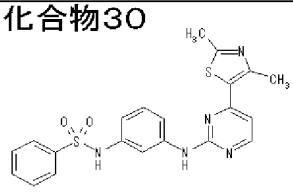
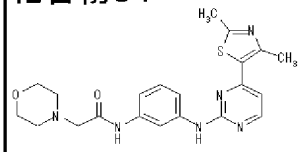
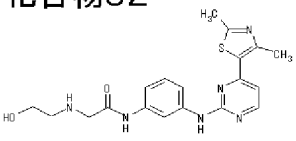
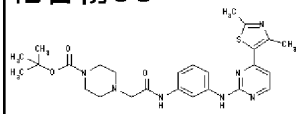
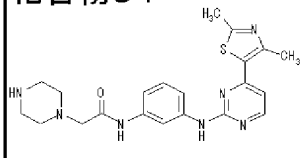
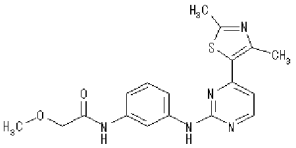
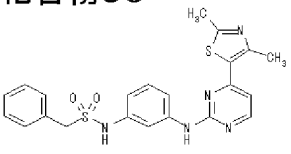
(0059)

Table 1.

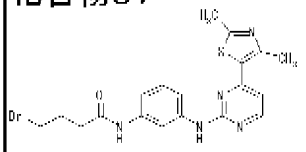
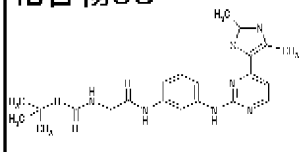
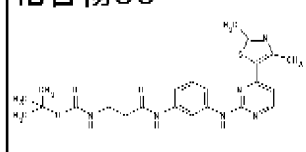
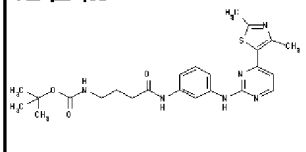
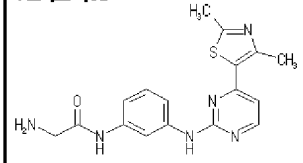
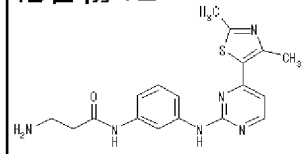
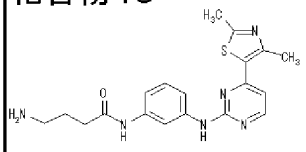
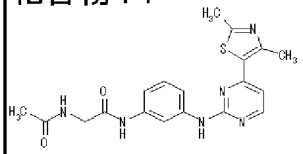
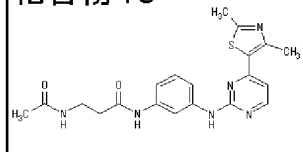
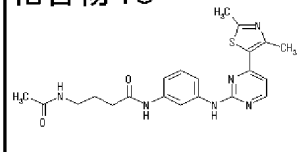
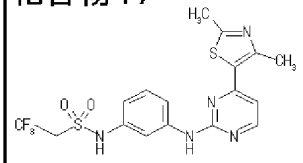
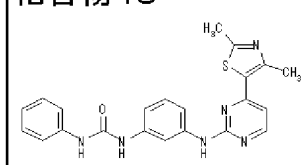
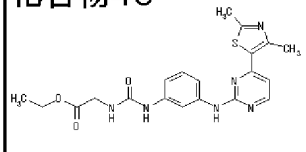
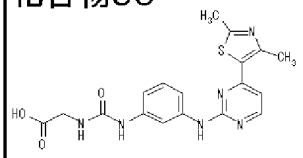
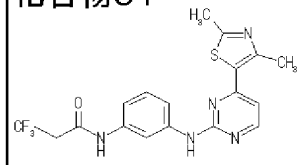
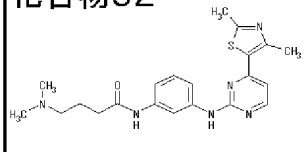
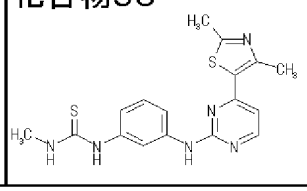
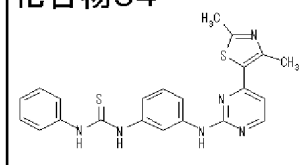
[0060]



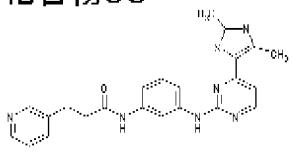
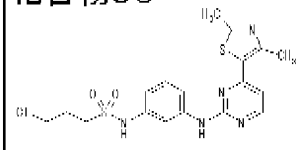
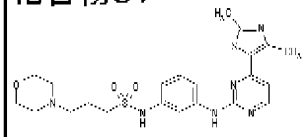
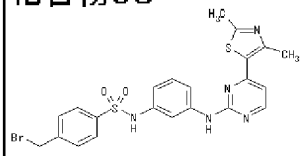
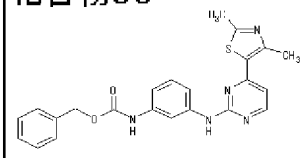
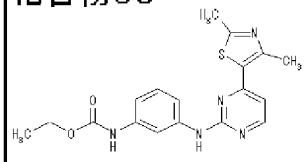
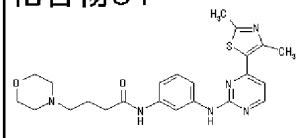
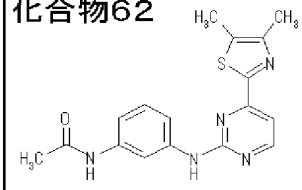
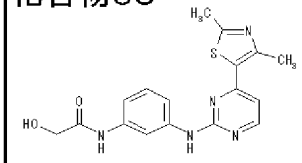
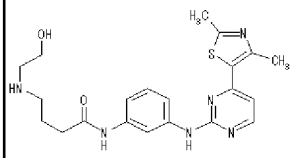
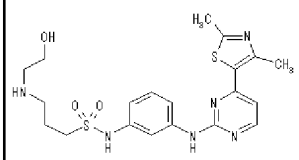
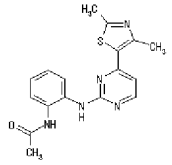
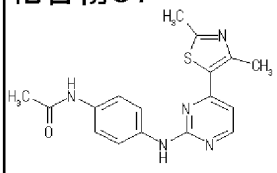
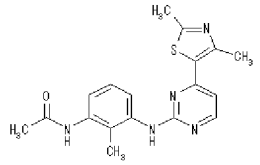
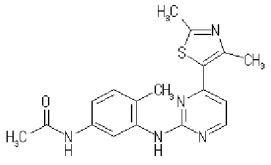
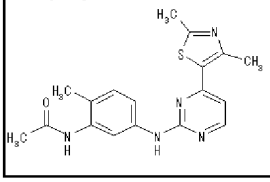
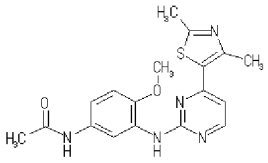
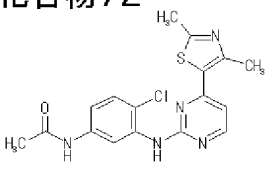
[0061] The Japanese characters before the numbers in each case mean "Compound"

化合物19 	化合物20 	化合物21 
化合物22 	化合物23 	化合物24 
化合物25 	化合物26 	化合物27 
化合物28 	化合物29 	化合物30 
化合物31 	化合物32 	化合物33 
化合物34 	化合物35 	化合物36 

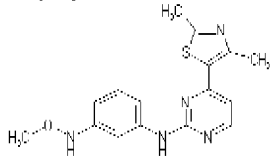
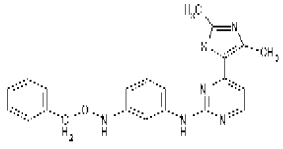
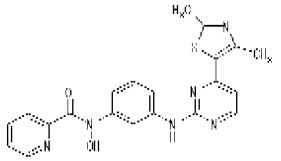
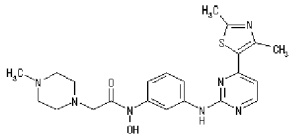
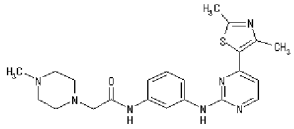
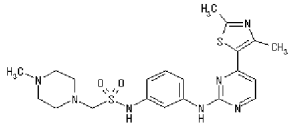
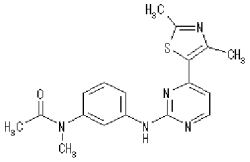
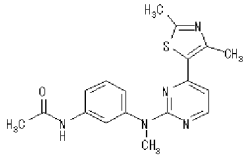
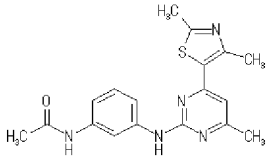
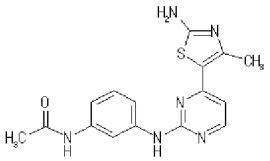
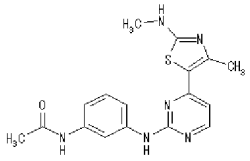
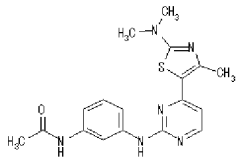
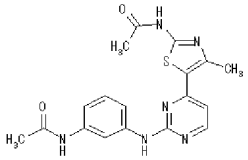
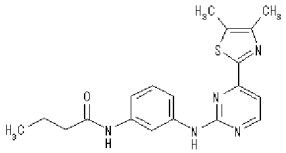
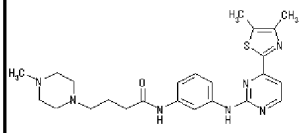
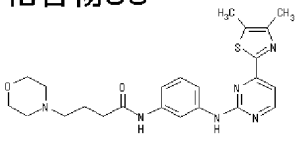
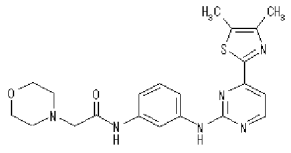
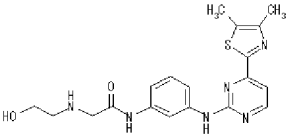
[0062] The Japanese characters before the numbers in each case mean "Compound"

化合物37 	化合物38 	化合物39 
化合物40 	化合物41 	化合物42 
化合物43 	化合物44 	化合物45 
化合物46 	化合物47 	化合物48 
化合物49 	化合物50 	化合物51 
化合物52 	化合物53 	化合物54 

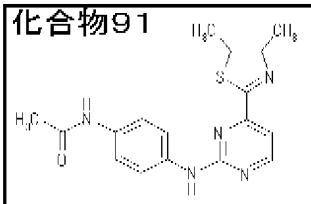
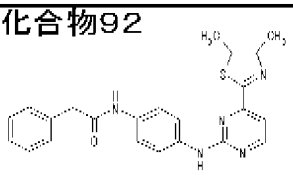
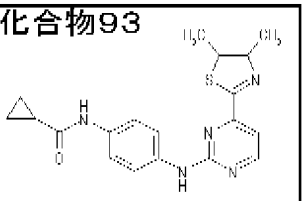
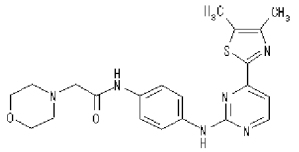
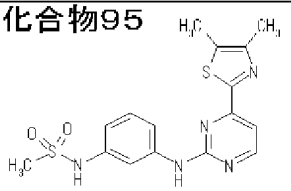
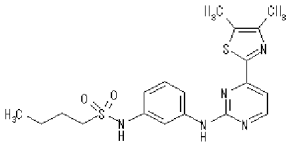
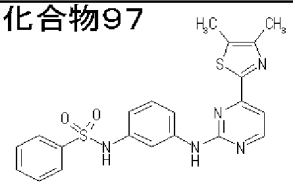
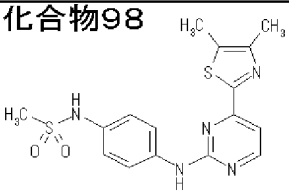
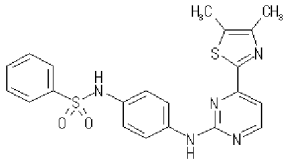
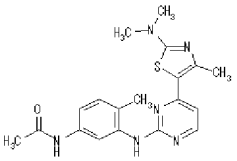
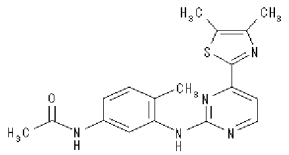
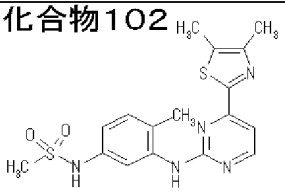
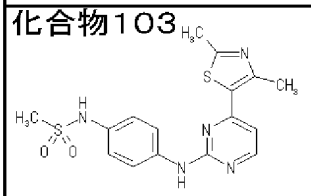
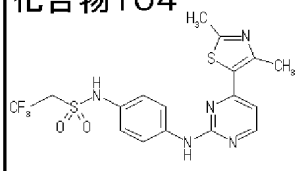
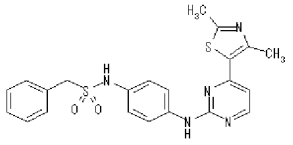
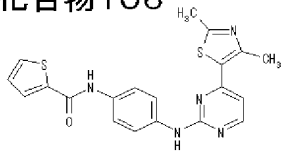
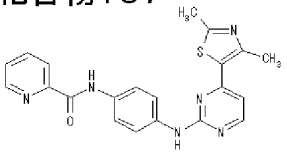
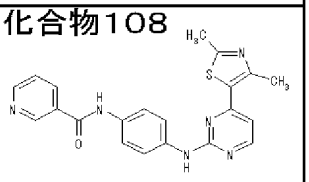
[0063] [化5]The Japanese characters below mean Compound

化合物55 	化合物56 	化合物57 
化合物58 	化合物59 	化合物60 
化合物61 	化合物62 	化合物63 
化合物64 	化合物65 	化合物66 
化合物67 	化合物68 	化合物69 
化合物70 	化合物71 	化合物72 

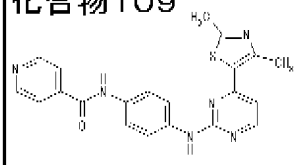
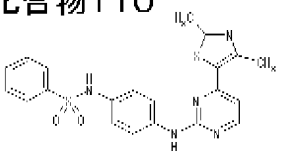
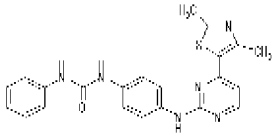
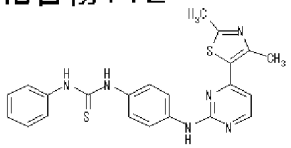
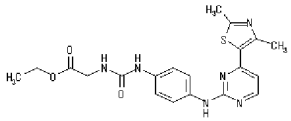
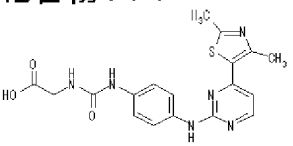
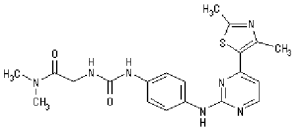
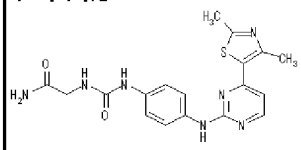
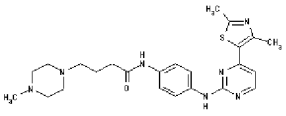
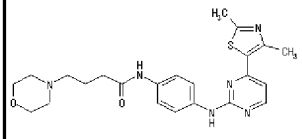
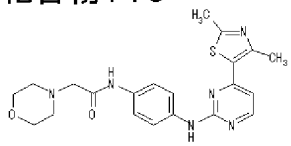
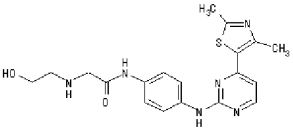
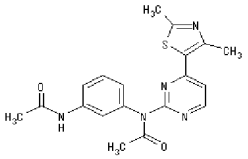
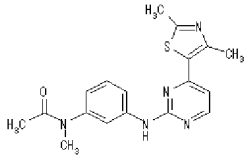
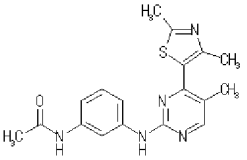
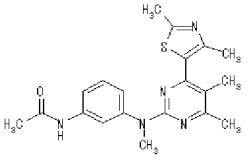
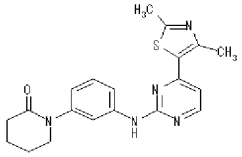
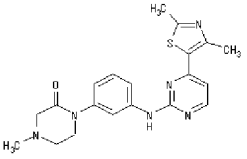
[0064] [化6] The Japanese characters below mean Compound

化合物73 	化合物74 	化合物75 
化合物76 	化合物77 	化合物78 
化合物79 	化合物80 	化合物81 
化合物82 	化合物83 	化合物84 
化合物85 	化合物86 	化合物87 
化合物88 	化合物89 	化合物90 

[0065] [化7] The Japanese characters below mean Compound

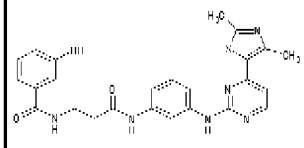
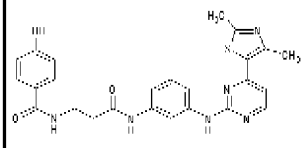
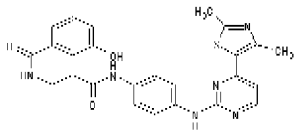
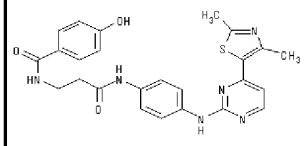
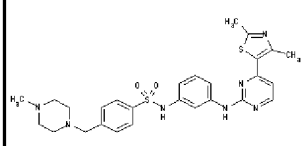
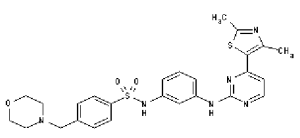
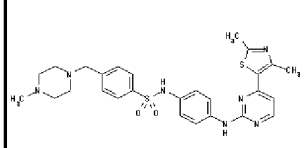
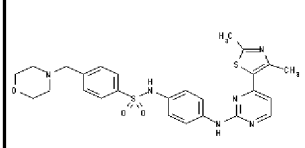
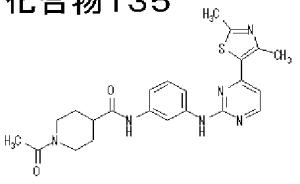
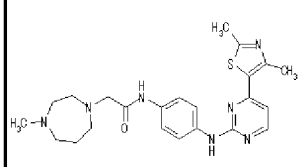
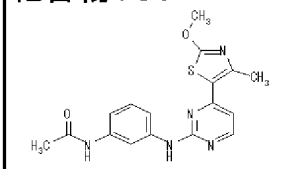
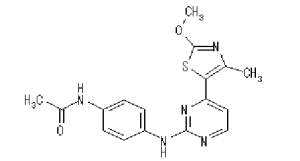
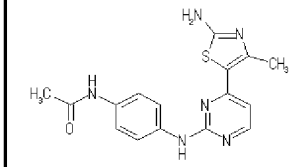
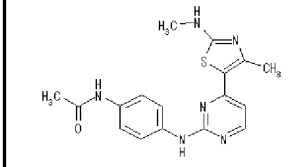
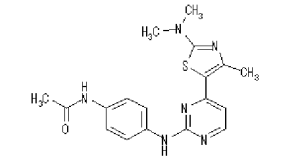
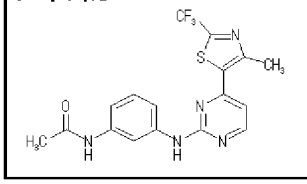
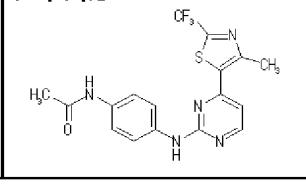
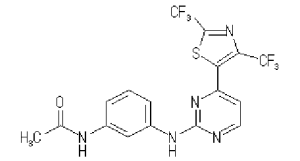
化合物91 	化合物92 	化合物93 
化合物94 	化合物95 	化合物96 
化合物97 	化合物98 	化合物99 
化合物100 	化合物101 	化合物102 
化合物103 	化合物104 	化合物105 
化合物106 	化合物107 	化合物108 

[0066] [化8] The Japanese characters below mean "Compound"

化合物109 	化合物110 	化合物111 
化合物112 	化合物113 	化合物114 
化合物115 	化合物116 	化合物117 
化合物118 	化合物119 	化合物120 
化合物121 	化合物122 	化合物123 
化合物124 	化合物125 	化合物126 

(0067)

The Japanese characters below mean Compound

127 	化合物128 	化合物129 
化合物130 	化合物131 	化合物132 
化合物133 	化合物134 	化合物135 
化合物136 	化合物137 	化合物138 
化合物139 	化合物140 	化合物141 
化合物142 	化合物143 	化合物144 

(0068)

As the medicinally permissible salt in compound of general formula (1) of this invention, acid addition salt of inorganic acid or organic acid may be proposed.

(0069)

Moreover, because the compound of this invention may be present as hydrate, aqueous adduct and solvate, moreover these hydrate, aqueous adduct and solvate are included in this invention, too.

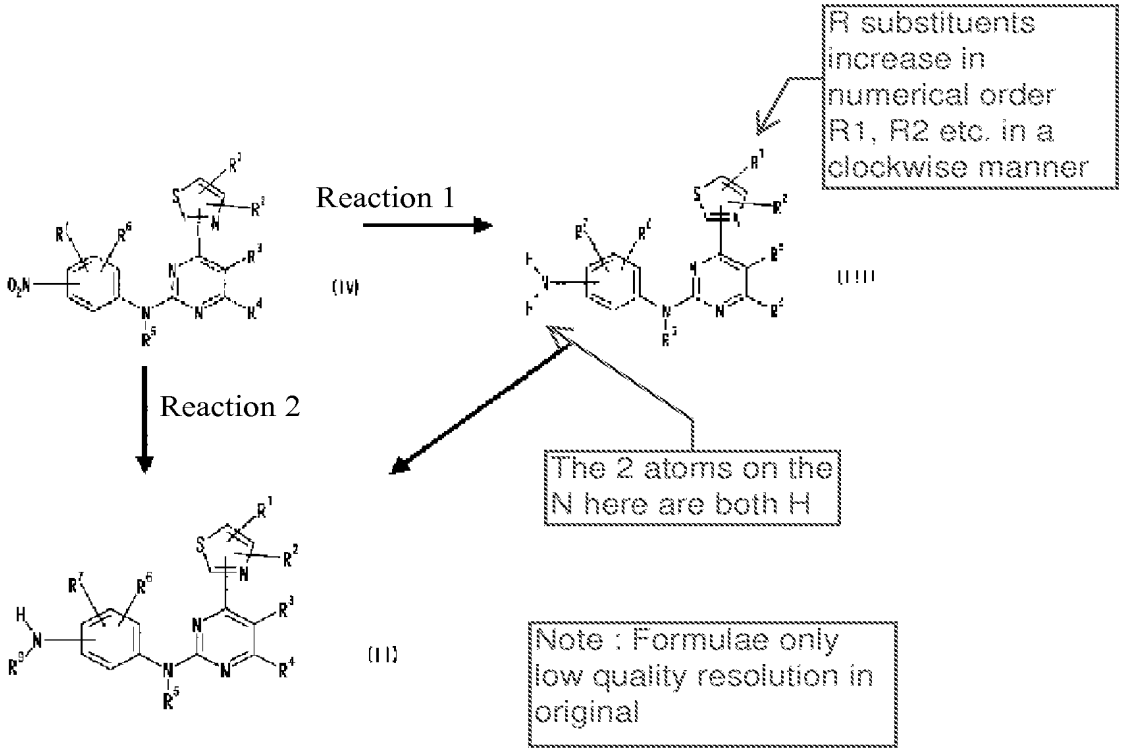
(0070)

Compound of general formula (1) of this invention can be produced using process described below.

(0071)

In the following general formula, unless limited in particular, R1, R2, R3, R4, R5, R6, R7 or R9 are as aforesaid.

(0072)



(0073)

1. Reaction 1.

The compound of the said general formula (III) can be prepared by reacting a compound represented by the aforesaid general formula (IV) (Shudong Wang et al, Jounal of Medicinal Chemistry, 47, 1662-1675, 2004) under suitable reduction conditions, in other words in the presence of catalyst such as iron or the like under conditions of 60°C to 100°C in suitable acid (for example acetic acid or hydrochloric acid or the like) and suitable solvent (for example ethanol, dioxane, water or arbitrary mixed solvent of these or the like) for 0 hours 30 minutes to 6 hours.

(0074)

It is possible to produce compound represented by the aforesaid general formula (II) (wherein, R9 denotes a group other than a hydrogen atom, hydroxy or alkoxy) by reacting compound represented by the aforesaid general formula (III) with X-R9' (wherein, R9' denotes a group with the same meaning as R9 except for a hydrogen atom hydroxy or alkoxy group, and X denotes a halogen atom or good leaving group) .

(0075)

Moreover, it is possible to produce compound represented by the aforesaid general formula (II) (wherein, R9 does not denote a hydrogen atom, hydroxy or alkoxy) by reacting a compound represented by the aforesaid general formula (III) with R16-CO-R17 (wherein, R16 and R17 are the same or different, and denote alkyl group which may have a suitable substituent, or one of R16 and R17 denotes a hydrogen atom), and thereafter, adding hydrogen.

2. Reaction 2.

Compound represented by the aforesaid general formula (II) (wherein, R9 denotes a hydrogen atom, hydroxy or alkoxy) can be produced by performing a hydrogenation reaction on a compound represented by the aforesaid general formula (IV) in the presence of palladium-carbon (Pd-C) in a suitable solvent (for example methanol, ethanol, water or arbitrary mixed solvent of these or the like) at room temperature condition for 1 hour to 12 hours .

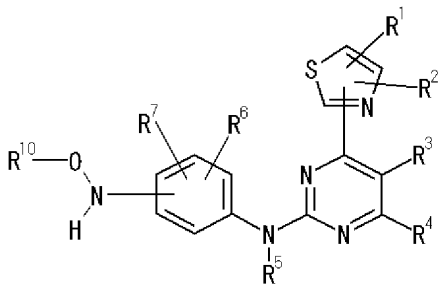
(0076)

Moreover, a compound represented by the aforesaid general formula (I) (wherein, R8 denotes COR10, CO2R10, CONR10R11, CSNR10R11 or SO2R10) can be produced by reacting the aforesaid compound represented by general formula (II) with any of the compounds X-COR10, X-CO2R10, R-NCO, R-NCS or X-SO2R10 (R10 is as aforesaid, and X denotes a halogen atom, hydroxy or good leaving group) or depending on circumstances by reacting further using a generally used alkylating agent.

(0077)

In addition, a compound represented by the following general formula (Ia) in which R8 in general formula (I) denotes OR10 can be produced by carrying out hydrogenation of a compound represented by the aforesaid general formula (IV) in the presence of palladium-carbon (Pd-C), reacting for 1 hour to 12 hours under room temperature condition in a suitable solvent (for example ethanol, ethanol, water or arbitrary mixed solvent of these or the like)

(0078)



(Ia)

(0079)

(wherein, R1, R2, R3, R4, R5, R6, R7 or R10 has the aforesaid meaning).

(0080)

Moreover, in suitable circumstances, in each of the aforesaid synthetic processes, each compound can be made into a derivative and converted to other compound using well-known process applicable to the field.

(0081)

In each of the aforesaid synthetic processes, protection of functional group or deprotection may sometimes be required. Suitable protecting group can be selected according to the type of functional group, using well-known process applicable to the field.

(0082)

Salt of cyanopyridine derivative represented by general formula (1), or solvate or hydrates thereof can be produced from cyanopyridine derivative using well known method.

(0083)

Compound of general formula (1) obtained using the aforesaid method or medicinally permitted salt, hydrate, aqueous adduct and solvate thereof have powerful aurora 2 kinase inhibitory action and are useful as cancer treatment and/or prevention drug.

(0084)

As for the administration method when using the compound of this invention as drug, a person skilled in the art can select suitably. For example, both administration pathways of oral administration or parenteral administration such as subcutaneous injection, intravenous injection, intramuscular injection, intraperitoneal injection or the like can be selected. The dose can suitably determined in accordance with conditions such as age of patient, state of health, body weight or the like, or when another drug is being given at the same time, condition such as the kind of drug and administration frequency, or whether a desired effect can be suitably mesured when administered. Generally daily administered amount of effective ingredient is 0.5-300mg/kg body weight, usual 1-30mg/kg weight, and it can be administered in a single dose or several doses per day.

(0085)

Moreover, when the compound of this invention is used as a drug, it is preferably be administered by preparing a medicinal composition including the aforesaid effective ingredient and one or more drug additive.

(0086)

As medicinal composition suitable for oral administration, for example, tablet, encapsulated formulation, powdered drug, liquid agent, elixir agent or the like may be proposed, and as a suitable medicinal composition for parenteral administration, for example a medicinal composition in the form of sterilized liquid such as liquid agent or suspension is possible.

(0087)

The kind of drug additive used in the preparation of the medicinal composition is not limited in particular, and suitable drug additive corresponding to a form of medicinal composition can be selected in various ways. Drug additive may be solid or liquid, and it is possible to use for example solid support or liquid carrier. As example of solid support, it is possible to use capsule of ordinary gelatin type. Moreover, for example, it can be tabletted together with one or more or drug additive or without using drug additive; or effective ingredient is prepared as powder, and encapsulated. In general these capsules, tablet, powder can include effective ingredient of 5-95 wt.% and preferably 5-90 wt.% with respect to total weight of a drug, and administration unit form may contain 5-500mg, preferably 25-250mg of effective ingredient. As liquid carrier, water, mineral oil, oil of animal or plant source such as peanut oil, soya bean oil, sesame oil or the like or synthetic oil is used.

(0088)

Moreover, generally, physiological saline, dextrol or similar sucrose solution, glycol species such as ethylene glycol, propylene glycol, polyethyleneglycol and the like are preferable as the liquid carrier, and particularly in the case of the injectable liquid using physiological saline, the preparation is usually carried out so that the effective ingredient is included at 0.5-20%, preferably 1-10% by weight.

Examples

(0089)

Hereinafter, this invention will be further described in greater detail by Production Example, Example and Pharmacology Test Example. However, this invention is not limited to these descriptions. Moreover, 1H-NMR was measured in DMSO-d6 at 300MHz or 400MHz, unless otherwise stated. For the chemical shift value of 1H-NMR, tetramethylsilane (TMS) was used as internal standard and the relative delta value is shown as parts per million (ppm). Coupling constant are shown in Hertz (Hz) for the evident multiplicity, and shown as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), brs (broad singlet). The column chromatography was carried out using silica gel made by Fuji Silysia Chemicals made by Merck Corp..

(0090)

Production Example 1.

3-nitrophenyl guanidine.

4N hydrochloric acid /1,4,-dioxane solution (63 mL) was added under ice cooling to 3-nitroaniline (20.0 g, 0.15 mole) and cyanamide (10.7g) dissolved in 1,4,-dioxane (150 mL) and the mixture was stirred at 80°C for four hours. 6N sodium hydroxide aqueous solution (50.7 mL) was added under ice cooling to the reaction liquid, and thereafter, 1,4,-dioxane was eliminated by distillation under reduced pressure. The precipitate was recovered by filtration, and it washed with water, and 3-nitrophenyl guanidine (23.8 g, 91 %) was obtained by drying under reduced pressure at 60°C.

1H-NMR: 7.60 (1H, m), 7.52 (1H, brs), 7.39 (1H, dd, 8Hz, 8 Hz), 7.16 (1H, d, J = 8 Hz), 5.41 (4H, brs).

(0091)

Production Example 2.

3-dimethylamino-1-(2,4-dimethyl thiazol-5-yl) propenone.

5-acetyl-2,4-dimethyl thiazole (20.0 g, 0.13 mole) was dissolved in 85 ml ethanol and N,N-dimethylformamide dimethylacetal (85.6 mL) was added and was heated under reflux for four hours. The reaction liquid was concentrated under reduced pressure, and 3-dimethylamino-1-(2,4-dimethyl thiazol-5-yl) propenone (18.9 g, 70 %) was obtained by adding diethyl ether to the residue, and recovering the precipitated crystals by filtration.

1H-NMR: 7.64 (1H, d, J = 12 Hz), 5.32 (1H, d, J = 12 Hz), 3.13 (3H, brs), 2.58 (3H, brs), 2.58 (3H, s), 2.55 (3H, s).

(0092)

Production Example 3.

(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl)-(3-nitro phenyl) amine.

3-dimethylamino-1-(2,4-dimethyl thiazol-5-yl) propenone (20.0 g, 0.095 mole) and 3-nitrophenyl guanidine (18.8 g) dissolved in 2-methoxy ethanol (400 mL) were heated under reflux for 20 hours. The reaction liquid was concentrated under reduced pressure, ethyl acetate was added to the residue, the precipitated crystals were recovered by filtration and (4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl)-(3-nitro phenyl) amine (22.5 g, 72 %) was obtained .

1H-NMR: 10.20 (1H, s), 8.92 (1H, m), 8.61 (1H, d, J = 5 Hz), 8.08 (1H, m), 7.82 (1H, m), 7.59 (1H, dd, J = 8Hz, 8 Hz), 7.20 (1H, d, J = 5 Hz), 2.67 (3H, s), 2.66 (3H, s).

(0093)

Production Example 4.

N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine.

Acetic acid (50 mL) suspension of iron powder (8.5 g) was stirred at 60°C for 30 minutes, and thereafter, water (150 mL) and a 1,4,-dioxane (500 mL) solution of (4-[2,4-dimethyl thiazol-5-yl]

pyrimidin-2-yl) (3-nitro phenyl) amine (10.0g, 30.5 mmol) were added, and the mixture was stirred at 60°C for one hour. After cooling, the reaction liquid was filtered, and the filtrate was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (8.2 g, 90 %) was obtained by adding diisopropyl ether to the residue, and recovering the precipitated crystals by filtration.
1H-NMR: 9.31 (1H, s), 8.47 (1H, d, J = 5 Hz), 7.01 (2H, m), 6.92 (2H, m), 6.22 (1H, m), 4.92 (2H, s), 2.65 (3H, s), 2.63 (3H, s).

(0094)

Example 1. Compound 1 of Table 1.

10 % palladium carbon (0.50 g) was added to N,N-dimethylformamide (100 mL) solution of (4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) -(3-nitro phenyl) amine (5.00g, 15.3 mmol) obtained by Production Example 3, and the mixture was stirred at room temperature under a hydrogen gas atmosphere for six hours 30 minutes. The reaction liquid was filtered, and water was added to filtrate, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) hydroxylamine (2.05 g, 43 %) was obtained by adding ethyl acetate and n-hexane to the residue, and recovering the precipitated crystals by filtration.
1H-NMR: 9.48 (1H, s), 8.49 (1H, d, J = 5 Hz), 8.22 (1H, d, J = 2 Hz), 8.18 (1H, s), 7.38 (1H, s), 7.18 (1H, d, J = 8 Hz), 7.05 (2H, m), 6.46 (1H, d, J = 8 Hz), 2.65 (3H, s), 2.63 (3H, s).

(0095)

Example 2. Compound 2 of Table 1.

Acetyl chloride (25ul) was added to tetrahydrofuran (5 mL) solution of triethylamine (53ul) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) hydroxylamine (0.10g, 0.32 mmol) obtained in Example 1, and it was stirred for three hours. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel chromatography (eluted with ethyl acetate) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N-hydroxyacetamide (0.04 g, 35 %) was obtained by crystallising it from acetic acid ethyl ester.
1H-NMR: 10.52 (1H, s), 9.71 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.01 (1H, s), 7.61 (1H, m), 7.26 (2H, m), 7.09 (1H, d, J = 5 Hz), 2.65 (3H, s), 2.64 (3H, s), 2.20 (3H, s).

(0096)

Example 3. Compound 3 of Table 1.

Acetyl chloride (48ul) was added to tetrahydrofuran (5 mL) solution of triethylamine (98ul) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) hydroxylamine (0.10g, 0.32 mmol) obtained in Example 1, and it was stirred for three hours. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel chromatography (eluted with ethyl acetate) and N-acetyl-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide (0.05 g, 42 %) was obtained by crystallising it from ether.

1H-NMR: 9.85 (1H, s), 8.55 (1H, d, J = 5 Hz), 7.97 (1H, brs), 7.76 (1H, d, J = 8 Hz), 7.38 (1H, dd, J = 8Hz, 8 Hz), 7.13 (1H, d, J = 5 Hz), 7.09 (1H, d, J = 8 Hz), 2.65 (3H, s), 2.64 (3H, s), 2.23 (3H, s), 2.06 (3H, s).

(0097)

Example 4. Compound 4 of Table 1.

Using N-butyryl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N-hydroxy butanamide was obtained by the same procedures as in the process for production of Compound 2 of Table 1.

1H-NMR: 10.40 (1H, s), 9.71 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.04 (1H, s), 7.59 (1H, d, J = 7 Hz), 7.28 (2H, m), 7.09 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 1.61 (2H, m), 0.94 (3H, J = 8 Hz).

(0098)

Example 5. Compound 5 of Table 1.

Using N-butyryl chloride, N-butyryl oxy-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 3 of Table 1.

1H-NMR: 9.87 (1H, s), 8.55 (1H, d, J = 5 Hz), 8.01 (1H, s), 7.74 (1H, d, J = 7 Hz), 7.39 (1H, m), 7.14 (1H, d, J = 5 Hz), 7.07 (1H, d, J = 8 Hz), 2.64 (6H, s), 2.28 (2H, m), 1.58 (4H, m), 0.90 (6H, m).

(0099)

Example 6. Compound 6 of Table 1.

Using benzoyl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N-hydroxybenzamide was obtained by the same procedures as in the process for production of Compound 2 of Table 1.

1H-NMR: 10.63 (1H, s), 9.77 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.12 (1H, s), 7.65 (2H, m), 7.59 (1H, m), 7.43 (3H, m), 7.29 (1H, dd, J = 8Hz, 8 Hz), 7.13 (1H, d, J = 9 Hz), 7.10 (1H, d, J = 5 Hz), 2.63 (3H, s), 2.58 (3H, s).

(0100)

Example 7. Compound 7 of Table 1.

Using benzoyl chloride, N-benzoyloxy-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) benzamide was obtained by the same procedures as in the process for production of Compound 3 of Table 1.

1H-NMR: 9.86 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.15 (1H, s), 8.02 (2H, d, J = 7 Hz), 7.76 (1H, t, J = 8 Hz), 7.66 (1H, m), 7.60 (4H, m), 7.45 (1H, m), 7.38 (2H, m), 7.31 (1H, dd, J = 8Hz, 8 Hz), 7.12 (1H, d, J = 5 Hz), 7.01 (1H, d, J = 8 Hz), 2.63 (3H, s), 2.61 (3H, s).

(0101)

Example 8. Compound 8 of Table 1.

Acetyl chloride (0.08 mL) was added to tetrahydrofuran (10 mL) solution of triethylamine (0.17 mL) and N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.30g, 1.01 mmol) obtained in Production Example 4, and it was left to stand at room temperature overnight. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide (0.23 g, 67 %) was obtained by adding ethyl acetate to the residue, and recovering the precipitated crystals by filtration.

1H-NMR: 9.83 (s, 1H), 9.61 (s, 1H), 8.50 (d, 1H, J = 5 Hz), 7.84 (s, 1H), 7.52 (m, 1H), 7.20 (m, 2H), 7.06 (d, IH, J = 5 Hz), 2.65 (s, 3H), 2.63 (s, 3H), 2.04 (3H, s).

(0102)

Example 9. Compound 9 of Table 1.

Using N-butyryl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.77 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.90 (1H, s), 7.47 (1H, m), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.28 (2H, t, J = 7 Hz), 1.62 (2H, m), 0.93 (3H, t, J = 7 Hz).

(0103)

Example 10. Compound 10 of Table 1.

Using isobutyryl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) isobutanamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.72 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.95 (1H, s), 7.44 (1H, m), 7.20 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.62 (1H, m), 1.10 (6HJ = 6 Hz).

(0104)

Example 11. Compound 11 of Table 1.

Using benzoyl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) benzamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.21 (1H, s), 9.67 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.15 (1H, s), 7.96 (2H, d, J = 7 Hz), 7.55 (4H, m), 7.29 (2H, m), 7.07 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.60 (3H, s).

(0105)

Example 12. Compound 12 of Table 1.

Using phenylacetyl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) phenylacetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.07 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.89 (1H, s), 7.50 (1H, m), 7.34 (4H, m), 7.24 (3H, m), 7.06 (1H, d, J = 5 Hz), 3.64 (2H, s), 2.63 (3H, s), 2.63 (3H).

(0106)

Example 13. Compound 13 of Table 1.

3-phenyl propionyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-3-phenyl propion amide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.81 (1H, s), 9.59 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.87 (1H, s), 7.50 (1H, d, J = 7 Hz), 7.26 (7H, m), 7.06 (1H, d, J = 5 Hz), 2.92 (2H, t, J = 8 Hz), 2.63 (6H, s), 2.62 (m).

(0107)

Example 14. Compound 14 of Table 1.

Cyclopropane carbonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) cyclopropane carboxamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.08 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.89 (1H, s), 7.49 (1H, m), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.82 (1H, m), 0.79 (4Hm).

(0108)

Example 15. Compound 15 of Table 1.

Cyclohexane carbonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) cyclohexane carboxamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.70 (1H, s), 9.59 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.94 (1H, s), 7.43 (1H, m), 7.20 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.35 (1H, m), 1.78 (4Hm), 1.65 (1H, m), 1.42 (2H, m), 1.23 (3H, m).

(0109)

Example 16. Compound 16 of Table 1.

Valeryl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) pentanamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.77 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.89 (1H, s), 7.47 (1H, m), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.31 (2H, t, J = 8 Hz), 1.58 (2H, m), 1.33 (2H, m), 0.91 (3H, t, J = 8 Hz).

(0110)

Example 17. Compound 17 of Table 1.

N-octanoyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) octanamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.76 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.89 (1H, s), 7.48 (1H, m), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.30 (2H, t, J = 8 Hz), 1.59 (2H, m), 1.29 (8H, m), 0.86 (3H, t, J = 7 Hz).

(0111)

Example 18. Compound 18 of Table 1.

2-thiophenecarbonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-thiophene carboxamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.19 (1H, s), 9.69 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.11 (1H, s), 8.04 (1H, d, J = 4 Hz), 7.85 (1H, d, J = 6 Hz), 7.54 (1H, m), 7.28 (2H, m), 7.23 (1H, m), 7.08 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.60 (3H, s).

(0112)

Example 19. Compound 19 of Table 1.

2-thiophene acetyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-(2-thienyl) acetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.11 (1H, s), 9.64 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.90 (1H, s), 7.51 (1H, m), 7.39 (1H, m), 7.23 (2H, m), 7.07 (1H, d, J = 5 Hz), 6.99 (2H, m), 3.88 (2H, s), 2.64 (3H, s), 2.63 (3H, s).

(0113)

Example 20. Compound 20 of Table 1.

Picolinoyl chloride hydrochloride (0.20 g) was added to etrahydrofuran (10 mL) solution of triethylamine (0.32 mL) and N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.30g, 1.01 mmol) obtained in Production Example 4, and the mixture was stirred at room temperature for three hours. Iced water was added to the reaction liquid, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) pyridine-2-carboxamide (0.30 g, 74 %) was obtained by recovering the precipitated crystals by filtration.

1H-NMR: 10.44 (1H, s), 9.71 (1H, s), 8.76 (1H, d, J = 4 Hz), 8.53 (1H, d, J = 5 Hz), 8.25 (1H, s), 8.18 (1H, d, J = 8 Hz), 8.09 (1H, m), 7.69 (1H, m), 7.52 (2H, m), 7.30 (1H, dd, J = 8Hz, 8 Hz), 7.09 (1H, d, J = 5 Hz), 2.65 (3H, s), 2.63 (3H, s).

(0114)

Example 21. Compound 21 of Table 1.

Nicotinoyl chloride hydrochloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) pyridine-3-carboxamide was obtained by the same procedures as in the process for production of Compound 20 of Table 1.

1H-NMR: 10.41 (1H, s), 9.71 (1H, s), 9.12 (1H, d, J = 2 Hz), 8.77 (1H, m), 8.52 (1H, d, J = 5 Hz), 8.29 (1H, m), 8.15 (1H, m), 7.57 (2H, m), 7.31 (2H, m), 7.08 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.61 (3H, s).

(0115)

Example 22. Compound 23 of Table 1.

BOP reagent (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (0.18 g) was added to N,N-dimethyl form amide (5 mL) solution of diisopropyl ethylamine (70ul), 5-methyl-2-thiophencarboxylic acid (53 mg), and N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.10g, 0.34 mmol) obtained in Production Example 4, and it was left to stand at room temperature overnight. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel chromatography (eluted with ethyl acetate : n-hexane = 2 : 1) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-(5-methyl thiophene e)-2-carboxamide (0.09 g, 65 %) was obtained by adding ethyl acetate and n-hexane, and recovering the precipitated crystals by filtration.

1H-NMR: 10.06 (1H, s), 9.67 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.08 (1H, s), 7.84 (1H, m), 7.53 (1H, m), 7.26 (2H, m), 7.08 (1H, d, J = 5 Hz), 6.92 (1H, m), 2.64 (3H, s), 2.61 (3H, s).

(0116)

Example 23. Compound 25 of Table 1.

2,4-dimethyl thiazole-5-carboxylic acid was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-(2,4-dimethyl thiazole)-5-carboxamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.

1H-NMR: 10.02 (1H, s), 9.68 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.06 (1H, s), 7.52 (1H, m), 7.23 (2H, m), 7.08 (1H, d, J = 5 Hz), 2.66 (3H, s), 2.63 (3H, s), 2.62 (3H, s), 2.55.

(0117)

Example 24. Compound 27 of Table 1.

Chloroacetyl chloride was used, and 2-chloro-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 10.21 (1H, s), 9.69 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.92 (1H, s), 7.54 (1H, m), 7.24 (2H, m), 7.08 (1H, d, J = 5 Hz), 4.25 (2H, s), 2.65 (3H, s), 2.64 (3H, s).

(0118)

Example 25. Compound 28 of Table 1.

Methanesulfonyl chloride (86ul) was added to tetrahydrofuran (10 mL) solution of triethylamine (0.17 mL) and N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.30g, 1.01 mmol) obtained in Production Example 4, and it was left to stand at room temperature for three hours. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) methane sulfonamide (0.29 g, 76 %) was obtained by adding diisopropyl ether to the residue, and recovering the precipitated crystals by filtration.

1H-NMR: 9.68 (1H, s), 9.65 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.61 (1H, m), 7.57 (1H, m), 7.25 (1H, dd, J = 8Hz, 8 Hz), 7.08 (1H, d, J = 5 Hz), 6.83 (1H, m), 3.00 (3H, s), 2.65 (3H, s), 2.64 (3H, s).

(0119)

Example 26. Compound 29 of Table 1.

N-butane sulphonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butane sulfonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 9.67 (2H, s), 8.50 (1H, d, J = 5 Hz), 7.57 (2H, m), 7.23 (1H, dd, J = 8Hz, 8 Hz), 7.08 (1H, d, J = 5 Hz), 6.82 (1H, d, J = 7 Hz), 3.09 (2H, t, J = 8 Hz), 1.67 (2H, m), 1.35 (2Hm), 0.83 (3H, t, J = 8 Hz).

(0120)

Example 27. Compound 30 of Table 1.

Benzenesulphonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) benzenesulphonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 10.18 (1H, s), 9.62 (1H, s), 8.49 (1H, d, J = 5 Hz), 7.80 (2H, d, J = 7 Hz), 7.53 (5H, m), 7.12 (1H, dd, J = 8Hz, 8 Hz), 7.06 (1H, d, J = 5 Hz), 6.68 (1H, d, J = 8 Hz), 2.65 (3H, s), 2.62 (3H, s).

(0121)

Example 28. Compound 31 of Table 1.

Potassium carbonate (70 mg) and catalytic quantity of potassium iodide were added to N,N-dimethylformamide solution (5 mL) of morpholine (47ul) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-chloroacetamide (0.10g, 0.27 mmol) obtained in Example 26, and the mixture was stirred at 80°C for two hours. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was purified using silica gel chromatography (eluted with chloroform:methanol = 19 : 1) and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-morpholine-4-yl acetamide (0.11 g, 96 %) was obtained.

1H-NMR: 9.61 (1H, s), 9.60 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.92 (1H, s), 7.49 (1H, d, J = 8 Hz), 7.24 (2H, m), 7.07 (1H, d, J = 5 Hz), 3.64 (4H, m), 3.13 (2H, s), 2.64 (3H, s), 2.64 (3H, s), 2.53 (4H, m).

(0122)

Example 29. Compound 32 of Table 1.

Ethanolamine was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-(2-hydroxyethyl amino) acetamide was obtained by the same procedures as in the process for production of Compound 31 of Table 1. Thereafter, hydrochloride was made by treating with 4N hydrochloric acid / ethyl acetate.

1H-NMR: 10.48 (1H, s), 9.72 (1H, s), 8.94 (2H, brs), 8.51 (1H, d, J = 5 Hz), 7.91 (1H, s), 7.58 (1H, m), 7.26 (2H, m), 7.09 (1H, d, J = 5 Hz), 3.71 (2H, t, J = 5 Hz), 3.10 (2H, m)2.66 (3H, s), 2.64 (3H, s).

(0123)

Example 30. Compound 33 of Table 1.

1-t-butoxycarbonyl piperazine was used, and 2-(4-t-butoxycarbonyl piperazine-1-yl)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by the same procedures as in the process for production of Compound 31 of Table 1.

1H-NMR: 9.60 (2H, s), 8.50 (1H, d, J = 5 Hz), 7.92 (1H, s), 7.49 (1H, d, J = 8 Hz), 7.24 (2H, m), 7.07 (1H, d, J = 5 Hz), 3.37 (4H, m), 3.16 (2H, s), 2.63 (6H, s), 1.40 (9H).

(0124)

Example 31. Compound 35 of Table 1.

Methoxyacetyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-methoxy acetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.62 (1H, s), 9.59 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.97 (1H, s), 7.51 (1H, d, J = 8 Hz), 7.24 (2H, m), 7.07 (1H, d, J = 5 Hz), 4.00 (2H, s), 3.39 (3H, s), 2.64 (3H, s)2.63 (3H, s).

Example 32. Compound 36 of Table 1.

Phenylmethane sulphonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) phenylmethane sulfonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 9.79 (1H, s), 9.70 (1H, s), 8.52 (1H, d, J = 5 Hz), 7.61 (2H, m), 7.35 (3H, m), 7.31 (2H, m), 7.25 (1H, dd, J = 8Hz, 8 Hz), 7.09 (1H, d, J = 5 Hz), 6.81 (1H, m), 4.47 (2H, s), 2.64 (3H, s), 2.62 (3H, s).

(0125)

Example 33. Compound 37 of Table 1.

4-bromo butyryl chloride was used, and 4-bromo-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.89 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.90 (1H, s), 7.49 (1H, m), 7.22 (2H, m), 7.06 (1H, d, J = 5 Hz), 3.60 (2H, t, J = 6 Hz), 2.65 (3H, s), 2.63 (3H, s), 2.12 (2H, m).

(0126)

Example 34. Compound 38 of Table 1.

N-t-butoxycarbonyl glycine was used, and 2-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.

1H-NMR: 9.80 (1H, s), 9.64 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.87 (1H, s), 7.52 (1H, m), 7.23 (2H, m), 7.06 (1H, d, J = 5 Hz), 6.99 (1H, t, J = 5 Hz), 3.73 (2H, d, J = 5 Hz), 2.65 (3Hs), 2.63 (3H, s), 1.40 (9H, s).

(0127)

Example 35. Compound 39 of Table 1.

N-t-butoxycarbonyl-β-alanine was used, and 3-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propanamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.
1H-NMR: 9.85 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.88 (1H, s), 7.50 (1H, d, J = 7 Hz), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 6.82 (1H, m), 3.22 (2H, dd, J = 6.13 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.38 (9H, s).

(0128)

Example 36. Compound 40 of Table 1.

N-t-butoxycarbonyl-y-amino butanoic acid was used, and 4-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.
1H-NMR: 9.80 (1H, s), 9.61 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.89 (1H, s), 7.48 (1H, d, J = 7 Hz), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 6.83 (1H, m), 2.97 (2H, dd, J = 6.13 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.30 (2H, t, J = 7 Hz), 1.70 (2H, m), 1.38 (9H, s).

(0129)

Example 37. Compound 41 of Table 1.

4N hydrochloric acid /1,4,-dioxane (5 mL) was added to 1,4,-dioxane (10 mL) solution of 2-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide (0.31g, 0.68 mmol) obtained in Example 34, and it was left to stand at room temperature overnight. The reaction liquid was concentrated under reduced pressure, and ethyl acetate was added to the residue, and 2-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide • hydrochloride (0.25 g, 94 %) was obtained by recovering the precipitate which formed by filtration.
1H-NMR: 10.50 (1H, s), 9.78 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.21 (3H, brs), 7.90 (1H, s), 7.58 (1H, m), 7.28 (2H, m), 7.10 (1H, d, J = 5 Hz), 3.78 (2H, m), 2.67 (3H, s), 2.65 (3H, s).

(0130)

Example 38. Compound 42 of Table 1.

3-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propanamide obtained in Example 35 was used, and 3-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propanamide was obtained by the same procedures as in the process for production of Compound 41 of Table 1.
1H-NMR: 10.11 (1H, s), 9.68 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.88 (4H, m), 7.52 (1H, d, J = 8 Hz), 7.26 (2H, m), 7.08 (1H, d, J = 5 Hz), 3.08 (2H, m), 2.73 (2H, t, J = 7 Hz), 2.66 (3H, s), 2.64 (3H, s).

(0131)

Example 39. Compound 43 of Table 1.

4-(t-butoxycarbonyl amino)-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide obtained in Example 36 was used, and 4-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 41 of Table 1.

1H-NMR: 9.96 (1H, s), 9.65 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.89 (4H, m), 7.51 (1H, d, J = 8 Hz), 7.23 (2H, m), 7.07 (1H, d, J = 5 Hz), 2.85 (2H, m), 2.66 (3H, s), 2.64 (3H, s), 2.44 (2H, t, J = 7 Hz), 1.87 (2H, m).

(0132)

Example 40. Compound 47 of Table 1.

Using 2,2,2-trifluoroethane sulphonyl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-(2,2,2-trifluoroethane) sulfonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 10.37 (1H, s), 9.69 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.67 (1H, m), 7.58 (1H, m), 7.27 (1H, dd, J = 8Hz, 8 Hz), 7.09 (1H, d, J = 5 Hz), 6.84 (1H, dd, J = 6.8 Hz), 4.46 (2H, J = 9 Hz), 2.65 (3H, s), 2.64 (3H, s).

(0133)

Example 41. Compound 48 of Table 1.

Phenyl isocyanate (40ul) was added to dichloromethane (5 mL) solution of the N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.10g, 0.34 mmol) obtained in production Example 4, and it was left to stand at room temperature overnight. The reaction liquid was concentrated under reduced pressure, and ethyl acetate was added to the residue, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N'-phenyl urea (0.1. g, 71 %) was obtained by recovering the precipitated crystals by filtration.

1H-NMR: 9.62 (1H, s), 8.64 (1H, s), 8.55 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.74 (1H, s), 7.45 (3H, m), 7.28 (2H, m), 7.20 (2H, m), 7.07 (1H, d, J = 5 Hz), 6.96 (1H, t, J = 7 Hz), 2.64 (3H, s), 2.62 (3H, s).

(0134)

Example 42. Compound 49 of Table 1.

Isocyanic acid acetic acid ethyl (sic) was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N'-ethoxycarbonylmethyl urea was obtained by the same procedures as in the process for production of Compound 48 of Table 1.

1H-NMR: 9.56 (1H, s), 8.67 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.62 (1H, s), 7.41 (1H, m), 7.15 (2H, m), 7.05 (1H, d, J = 5 Hz), 6.46 (1H, t, J = 6 Hz), 4.12 (2H, q, J = 7 Hz), 3.87 (2Hd.J= 6 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.21 (t, J = 7 Hz).

(0135)

Example 43. Compound 50 of Table 1.

4M lithium hydroxide aqueous solution (0.59 mL) was added to tetrahydrofuran (6 mL) and methanol (4 mL) solution of the N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N'-ethoxycarbonylmethyl urea (0.20g, 0.47 mmol) obtained in Example 42, and the mixture was stirred at 60°C for 30 minutes. The reaction liquid was cooled to room temperature, and thereafter, water and 1N hydrochloric acid aqueous solution were added, and liquid property was made acidic, and it was left to stand at room temperature. (3-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) ureido) acetic acid (0.17 g, 91 %) was obtained by recovering the precipitate which formed by filtration.

1H-NMR: 12.52 (1H, brs), 9.55 (1H, s), 8.64 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.61 (1H, s), 7.39 (1H, m), 7.16 (2H, m), 7.05 (1H, d, J = 5 Hz), 6.37 (1H, t, J = 6 Hz), 3.80 (2H, d, J = 6 H), 2.65 (3H, s), 2.64 (3H, s).

(0136)

Example 44. Compound 51 of Table 1.

3,3,3-trifluoro propionic acid was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-(3,3,3-trifluoropropane) amide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.

1H-NMR: 10.20 (1H, s), 9.69 (1H, s), 8.52 (1H, d, J = 5 Hz), 7.92 (1H, s), 7.54 (1H, d, J = 8 Hz), 7.25 (2H, m), 7.08 (1H, d, J = 5 Hz), 3.51 (2H, q, J = 9 Hz), 2.64 (3H, s), 2.64 (3H, s).

(0137)

Example 45. Compound 52 of Table 1.

BOP reagent (benzotriazol-1-yloxy) (0.18 g) was added to N,N-dimethyl formamide (5 mL) solution of diisopropyl ethylamine (140ul), 4-(dimethylamino) butanoic acid hydrochloride (62 mg), and N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine (0.10g, 0.34 mmol) obtained in Production Example 4, and it was left to stand at room temperature overnight. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. The residue was dissolved in ethyl acetate, and thereafter, 4N hydrochloric acid / ethyl acetate solution was added, and the solvent was eliminated by distillation under reduced pressure. Ethyl acetate was added to the residue, and 4-dimethylamino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide • hydrochloride (0.06 g, 39 %) was obtained by recovering the precipitation by filtration.

1H-NMR: 10.35 (1H, brs), 10.02 (1H, s), 9.69 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.88 (1Hs), 7.51 (1H, d, J = 9 Hz), 7.24 (2H, m), 7.08 (1H, d, J = 5 Hz), 3.07 (2H, m), 2.76 (3H, s2.75 (3H, s), 2.66 (3H, s), 2.64 (3H, s)).

(0138)

Example 46. Compound 53 of Table 1.

Iso thiocyanic acid methyl ester was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N'-methylthio urea was obtained by the same procedures as in the process for production of Compound 48 of Table 1.

1H-NMR: 9.72 (1H, s), 9.48 (1H, brs), 8.53 (1H, d, J = 5 Hz), 7.83 (1H, s), 7.60 (1H, brs), 7.55 (1H, d, J = 8 Hz), 7.25 (1H, dd, J = 8Hz, 8 Hz), 7.10 (1H, d, J = 5 Hz), 6.92 (1Hd, J = 8 Hz), 2.90 (3H, d, J = 4 Hz), 2.66 (3H, s), 2.64 (3H, s).

(0139)

Example 47. Compound 55 of Table 1.

3-(3-pyridyl) propionic acid was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-3-(pyridin-3-yl) propanamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.

1H-NMR: 9.84 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.40 (1H, d, J = 5 Hz), 7.86 (1H, s), 7.67 (1H, d, J-8 Hz), 7.50 (1H, m), 7.31 (1H, m), 7.21 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.94 (2H, t, J = 8 Hz), 2.66 (2H, t, J = 8 Hz), 2.64 (3H, s), 2.63 (3H, s).

(0140)

Example 48. Compound 56 of Table 1.

Using 3-chloropropane sulphonyl chloride, 3-chloro-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propane sulfonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 9.81 (1H, s), 9.69 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.59 (2H, m), 7.25 (1H, dd, J = 8Hz, 8 Hz), 7.09 (1H, d, J = 5 Hz), 6.83 (1H, d, J = 8 Hz), 3.73 (2H, t, J = 6 Hz), 3.24 (2Hm), 2.65 (3H, s), 2.64 (3H, s), 2.14 (2H, m).

(0141)

Example 49. Compound 58 of Table 1.

Using 4-(bromomethyl) benzenesulphonyl chloride, N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-4-bromomethyl benzenesulphonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 10.24 (1H, s), 9.66 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.80 (2H, m), 7.55 (4H, m), 7.13 (1H, dd, J = 8Hz, 8 Hz), 7.07 (1H, d, J = 5 Hz), 6.68 (1H, d, J = 8 Hz), 4.74 (2H, d, J = 34 Hz), 2.65 (3H, s), 2.62 (3H, s).

(0142)

Example 50. Compound 59 of Table 1.

Chloro carboxylic acid benzyl ester was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) benzyloxy carboxamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.68 (1H, s), 9.60 (1H, s), 8.49 (1H, d, J = 5 Hz), 7.82 (1H, s), 7.42 (6H, m), 7.19 (1H, dd, J = 8Hz, 8 Hz), 7.06 (1H, d, J = 5 Hz), 5.15 (2H, s), 2.63 (6H, s).

(0143)

Example 51. Compound 60 of Table 1.

Chloro carboxylic acid ethyl ester was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) ethoxy carboxamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.59 (1H, s), 9.50 (1H, s), 8.49 (1H, d, J = 5 Hz), 7.81 (1H, s), 7.46 (1H, d, J = 8 Hz), 7.18 (1H, dd, J = 8Hz, 8 Hz), 7.05 (2H, m), 4.12 (2H, q, J = 7 Hz), 2.64 (3H, s), 2.63 (3H, s), 1.25 (3H, t, J = 7 Hz).

(0144)

Example 52. Compound 62 of Table 1.

Using 3-acetamidophenyl guanidine and 3-dimethylamino-1-(4,5-dimethyl thiazol-2-yl) propenone obtained in Production Example 2, N-(3-(4-[4,5-dimethyl thiazol-2-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by same procedure as in Reference Example 3.

1H-NMR: 9.83 (1H, s), 9.73 (1H, s), 8.53 (1H, m), 7.82 (1H, s), 7.55 (1H, m), 7.33 (1Hm), 7.21 (2H, m), 2.42 (3H, s), 2.34 (3H, s), 2.02 (3H, s).

(0145)

Example 53. Compound 67 of Table 1.

Using N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,4-diamine obtained in Production Example 4, N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.80 (1H, s), 9.54 (1H, s), 8.48 (1H, d, J = 5 Hz), 7.66 (2H, d, J = 9 Hz), 7.49 (2H, d, J = 9 Hz), 7.04 (1H, d, J = 5 Hz), 2.65 (3H, s), 2.63 (3H, s), 2.02 (3H, s).

(0146)

Example 54. Compound 82 of Table 1.

3-acetamidophenyl guanidine and N'-(5-(3-dimethylamino acryloyl)-4-methylthiazol-2-yl)-N,N-dimethylformamidine obtained by the process of Shudong Wang et al. (Jounal of Medicinal Chemistry, 47, 1662-1675, 2004) were used, and N-(3-(4-[2-amino-4-methylthiazol-5-yl]

pyrimidine-2-ylamino) phenyl) acetamide was obtained by same procedure as in Production Example 3.

1H-NMR: 9.82 (1H, s), 9.37 (1H, s), 8.29 (1H, d, J = 5 Hz), 7.72 (1H, s), 7.54 (1H, d, J = 8 Hz), 7.47 (2H, s), 7.16 (2H, m), 6.83 (1H, d, J = 5 Hz), 2.42 (3H, s), 2.01 (3H, s).

(0147)

Example 55. Compound 83 of Table 1.

3-acetamidophenyl guanidine and 3-dimethylamino-1-(4-methyl-2-methylamino thiazol-5-yl) propenone obtained by same process as in Production Example 2 was used, and N-(3-(4-[4-methyl-2-methylamino thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by same procedure as in Production Example 3.

1H-NMR: 9.81 (1H, s), 9.37 (1H, s), 8.29 (1H, d, J = 5 Hz), 8.01 (1H, d, J = 5 Hz), 7.78 (1H, s), 7.47 (1H, J = 8 Hz), 7.16 (2H, m), 6.85 (1H, d, J = 6 Hz), 2.83 (3H, d, J = 5 Hz), 2.45 (3H, s), 2.01 (3H, s).

(0148)

Example 56. Compound 103 of Table 1.

The N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,4-diamine obtained in Example 1 was used, and N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) methane sulfonamide was obtained by the same procedures as in the process for production of Compound 28 of Table 1.

1H-NMR: 9.64 (1H, s), 9.42 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.73 (2H, d, J = 9 Hz), 7.16 (2H, d, J = 9 Hz), 7.07 (1H, d, J = 5 Hz), 2.93 (3H, s), 2.66 (3H, s), 2.63 (3H, s).

(0149)

Example 57. Compound 104 of Table 1.

Using 2,2,2-trifluoroethane sulphonyl chloride, N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-(2,2,2-trifluoroethane) sulfonamide was obtained by the same procedures as in the process for production of Compound 103 of Table 1.

1H-NMR: 10.15 (1H, s), 9.68 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.75 (2H, d, J = 8 Hz), 7.17 (2H, d, J = 8 Hz), 7.09 (1H, d, J = 5 Hz), 4.41 (2H, q, J = 9 Hz), 2.66 (3H, s), 2.63 (S).

(0150)

Example 58. Compound 105 of Table 1.

Phenylmethane sulphonyl chloride was used, and N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) phenylmethane sulfonamide was obtained by the same procedures as in the process for production of Compound 103 of Table 1.

1H-NMR: 9.63 (1H, s), 9.59 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.72 (2H, d, J = 9 Hz), 7.33 (5H, m), 7.15 (2H, d, J = 9 Hz), 7.07 (1H, d, J = 5 Hz), 4.39 (2H, s), 2.66 (3H, s), 2.63 (3H, s).

(0151)

Example 59. Compound 106 of Table 1.

2-thiophenecarbonyl chloride was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-thiophene carboxamide was obtained by the same procedures as in the process for production of Compound 67 of Table 1.

1H-NMR: 10.14 (1H, s), 9.64 (1H, s), 8.51 (1H, d, J = 5 Hz), 8.00 (1H, d, J = 3 Hz), 7.83 (1H, d, J = 6 Hz), 7.74 (2H, d, J = 8 Hz), 7.64 (2H, d, J = 8 Hz), 7.22 (1H, dd, J = 3Hz, 6 Hz), 7.07 (1H, d, J = 5 Hz), 2.66 (3H, s), 2.64 (3H, s).

(0152)

Example 60. Compound 54 of Table 1.

Phenyl isothiocyanate was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-N'-phenylthio urea was obtained by the same procedures as in the process for production of Compound 48 of Table 1.

1H-NMR: 9.74 (1H, s), 9.70 (1H, s), 9.67 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.91 (1H, s)7.57 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 7.29 (3H, m), 7.09 (3H, m), 2.64 (3H, s), 2.62 (3H, s).

(0153)

Example 61. Compound 26 of Table 1.

3-chlorothiophene-2-carboxylic acid was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-(3-chlorothiophene) carboxamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.

1H-NMR: 10.10 (1H, s), 9.70 (1H, s), 8.52 (1H, d, J = 5 Hz), 8.10 (1H, s), 7.91 (1H, d, J = 5 Hz), 7.52 (1H, m), 7.28 (2H, m), 7.21 (1H, d, J = 5 Hz), 7.09 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.62 (3H, s).

(0154)

Example 62. Compound 44 of Table 1.

Acetyl chloride (0.02 mL) was added to tetrahydrofuran (5 mL) solution of triethylamine (0.06 mL) and 2-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide • hydrochloride (0.10g, 0.26 mmol) obtained in Example 37, and it was left to stand at room temperature overnight. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. 2-acetylamino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide (0.06 g, 58 %) was obtained by adding ethyl acetate to the residue, and recovering the precipitated crystals by filtration.

1H-NMR: 9.86 (1H, s), 9.64 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.16 (1H, m), 7.88 (1H, s), 7.52 (1H, m), 7.23 (2H, m), 7.07 (1H, d, J = 5 Hz), 3.87 (2H, d, J = 6 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.89 (3H, s).

(0155)

Example 63. Compound 45 of Table 1.

3-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propanamide obtained in Example 38 was used, and 3-acetylamino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propanamide was obtained by the same procedures as in the process for production of Compound 44 of Table 1.

1H-NMR: 9.86 (1H, s), 9.64 (1H, s), 8.50 (1H, d, J = 5 Hz), 8.16 (1H, m), 7.88 (1H, s), 7.52 (1H, m), 7.23 (2H, m), 7.07 (1H, d, J = 5 Hz), 3.87 (2H, d, J = 6 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.89 (3H, s).

(0156)

Example 64. Compound 46 of Table 1.

4-amino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide obtained in Example 39 was used, and 4-acetylamino-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) butanamide was obtained by the same procedures as in the process for production of Compound 44 of Table 1.

1H-NMR: 9.86 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 5 Hz), 7.92 (1H, m), 7.87 (1H, s), 7.50 (1H, d, J = 8 Hz), 7.23 (2H, m), 7.06 (1H, d, J = 5 Hz), 2.65 (3H, s), 2.63 (3H, s), 1.79 (3H, s).

(0157)

Example 65. Compound 119 of Table 1.

Chloroacetyl chloride was used, and 2-chloro-N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide was obtained by the same procedures as in the process for production of Compound 67 of Table 1. Furthermore, N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-morpholine-4-yl acetamide was obtained by the same procedures as in the process for production of Compound 31 of Table 1. Thereafter, hydrochloride was made by treating with 4N hydrochloric acid / ethyl acetate.

1H-NMR: 9.60 (1H, s), 9.58 (1H, s), 8.49 (1H, d, J = 5 Hz), 7.69 (2H, d, J = 9 Hz), 7.55 (2H, d, J = 9 Hz), 7.06 (1H, d, J = 5 Hz), 3.65 (4H, m), 3.11 (2H, s), 2.65 (3H, s), 2.63 (3H, s).

(0158)

Example 66. Compound 120 of Table 1.

2-chloro-N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) acetamide obtained in Example 65 was used, and N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-2-(2-

hydroxyethyl amino) acetamide was obtained by the same procedures as in the process for production of Compound 32 of Table 1. Thereafter, hydrochloride was made by treating with 4N hydrochloric acid / ethyl acetate.
1H-NMR: 10.56 (1H, s), 9.69 (1H, s), 8.95 (2H, brs), 8.51 (1H, d, J = 5 Hz), 7.72 (2H, J = 9 Hz), 7.54 (2H, d, J = 9 Hz), 7.08 (1H, d, J = 5 Hz), 3.96 (2H, m), 3.10 (2H, m), 2.67 (3H, s), 2.64 (3H, s).

(0159)

Example 67. Compound 108 of Table 1.

Nicotinic acid chloride was used, and N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) nicotinamide was obtained by the same procedures as in the process for production of a compound 67 of Table 1.
1H-NMR: 10.40 (1H, s), 9.66 (1H, s), 9.11 (1H, d, J = 2 Hz), 8.76 (1H, dd, J = 2Hz, 5 Hz), 8.51 (1H, d, J = 5 Hz), 8.31 (1H, dt, J = 2Hz, 8 Hz), 7.76 (2H, d, J = 8 Hz), 7.70 (2H, d, J = 8 Hz), 7.57 (1H, dd, J = 5Hz, 8 Hz), 7.07 (1H, d, J = 5 Hz), 2.66 (3H, s), 2.65 (3H, s).

(0160)

Example 68. Compound 135 of Table 1.

1-acetyl piperidine-4-carboxylic acid was used, and N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) 1-acetyl piperidine-4-carboxamide was obtained by the same procedures as in the process for production of Compound 23 of Table 1.
1H-NMR: 9.85 (1H, s), 9.62 (1H, s), 8.50 (1H, d, J = 4 Hz), 7.47 (1H, dt, J = 2Hz, 8 Hz), 7.22 (2H, m), 7.06 (1H, d, J = 4 Hz), 4.41 (1H, m), 3.88 (1H, m), 3.05 (1H, m), 2.66 (3H, s), 2.65 (3H, s), 2.65-2.55 (2H, m), 2.01 (3H, s), 1.85-1.70 (2H, m), 1.60 (1H, m)1.45 (1H, m).

(0161)

Example 69. Compound 57 of Table 1.

Morpholine (10 mL) was added to 3-chloro-N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl) propane sulfonamide (0.23g, 0.52 mmol) obtained in Example 48, and it was left to stand at 70°C overnight. Water was added to the reaction liquid, and extraction was carried out with ethyl acetate and was dried with magnesium sulfate, and thereafter the solvent was eliminated by distillation under reduced pressure. N-(4-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino) phenyl)-3-morpholino propane sulfonamide (0.18 g, 70 %) was obtained by adding ethyl acetate to the residue, and recovering the precipitated crystals by filtration.
1H-NMR: 9.78 (1H, s), 9.73 (1H, s), 8.51 (1H, d, J = 5 Hz), 7.64-7.56 (2H, m), 7.24 (1Hd, J = 8 Hz), 7.09 (1H, d, J = 5 Hz), 6.83 (1H, t, J = 8 Hz), 3.41 (4H, s), 3.16 (2H, t, J = 6 Hz), 2.65 (3H, s), 2.64 (3H, s)2.30 (2H, t, J = 6 Hz), 2.19 (4H, s), 1.82 (2H, m).

(0162)

Example 70. Compound 70 of Table 1.

4-methyl-N-(4-[2,4-dimethyl thiazol-5-yl] pyrimidin-2-yl) benzene-1,3-diamine was obtained using the same process as in Production Example 3 and 4 using 4-methyl-3-nitrophenyl guanidine. Using the aforesaid obtained compound, N-(5-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino)-2-methylphenyl) acetamide was obtained by the same procedures as in the process for production of Compound 8 of Table 1.

1H-NMR: 9.57 (1H, s), 9.28 (1H, s), 8.49 (1H, d, J = 5 Hz), 7.76 (1H, s), 7.53 (1H, d, J = 8 Hz), 7.11 (1H, d, J = 8 Hz), 7.05 (1H, d, J = 5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.13s), 2.05 (3H, s).

(0163)

Example 71. Compound 69 of Table 1.

N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino)-4-methylphenyl) acetamide was obtained by the same procedures as in the process for production of Compound 70 of Table 1 using 2-methyl-5-nitrophenyl guanidine.

1H-NMR: 9.80 (1H, s), 8.86 (1H, s), 8.39 (1H, d, J = 5 Hz), 7.63 (1H, d, J = 2 Hz), 7.31 (1H, dd, J = 2Hz&8 Hz), 7.12 (1H, d, J = 8 Hz), 6.95 (1H, d, J = 5 Hz), 2.61 (3H, s), 2.54 (3H, s), 2.14 (3H, s), 2.01 (3H, s).

(0164)

Example 72. Compound 68 of Table 1.

N-(3-(4-[2,4-dimethyl thiazol-5-yl] pyrimidine-2-ylamino)-2-methylphenyl) acetamide was obtained by the same procedures as in the process for production of Compound 70 of Table 1 using 2-methyl-3-nitrophenyl guanidine.

1H-NMR: 9.32 (1H, s), 8.90 (1H, s), 8.38 (1H, d, J = 5 Hz), 7.25 (1H, d, J = 2 Hz), 7.18 (1H, d, J = 8 Hz), 7.12 (1H, t, J = 8 Hz), 6.95 (1H, d, J = 5 Hz), 2.61 (3H, s), 2.55 (s), 2.07 (3H, s), 2.05 (3H, s).

(0165)

Pharmacology Test Example 1. Aurora 2 kinase activity inhibiting action.

(1). Preparation of aurora 2 kinase.

Total RNA was extracted from HeLa cell (ATCC No.CCL-2) according to normal method, and cDNA was synthesised by reverse transcriptase reaction. PCR was carried out using the aforesaid cDNA as the template. Primer sequence supplied to PCR is Sequence Number 1 (5'-GGA ATT CCA TAT GGA CCG ATC TAA AGA AAA CTG-3') and Sequence Number 2 (5'-GGG GGG CTC GAG AGA CTG TTT GCT AGC TGA TTC-3').

(0166)

The sequence obtained using the aforesaid PCR was identical to the sequence of aurora 2 kinase coding gene reported in the literature (The EMBO Journal Vol. 17 No.11 p3052-3065, 1998) quoted previously.

(0167)

The amplified aurora 2 kinase coding gene was introduced into the Escherichia coli expression vector pET32a (made by Novagen) to produce a recombinant. The recombinant can be obtained in accordance with 'Experimental Manual of Molecular Cloning' second edition (1989 Cold Spring Harbor Laboratory press) of Ambrook et al. and 'Current Protocols in Molecular Biology' (1999 John Wiley and Sons Inc) of Ausubel et al.

(0168)

Thereafter, recombinant was introduced into Escherichia coli BL21R strain (Novagen company) for expression of a large quantity of protein, and Escherichia coli strain for expression of a large quantity of aurora 2 kinase was produced.

(0169)

Escherichia coli strain for expression of a large quantity of aurora 2 kinase was cultured in LB culture medium which contained Ampicillin (50ug/mL). After shaking culture at 37°C for one hour, culture temperature was set to 25°C in order to induce expression of aurora 2 kinase, and IPTG (SIGMA Company) was added to give final concentration 0.1 mM, and it was shake-cultured at 25°C for 24 hours. Thereafter, culture liquid was separated by centrifugation at 7000 rpm for 10 minutes and separated culture medium, to recover the bacteria.

(0170)

Recovered bacteria were suspended in 36 mL of lysis buffer [50 mM Tris pH 6.8, 150 mM NaC1, 20 mM β-Glycerophosphate, 0.3 mM Na3VO4,50 mM NaF, 2 mM PMSF (phenylmethyl sulphonyl fluoride), one tablet of protease inhibitor cocktail (Boehringer Mannheim Co)], and pulverisation with ultrasound was carried out. Moreover, 4 mL of 10% NP-40 (Wako Junyaku) was added to dissociate non-specifical bonding between proteins.

(0171)

Thereafter, recombinant aurora 2 kinase in the liquid was adsorbed onto Ni-NTA agarose beads (QIAGEN company), and the beads with the recombinant aurora 2 kinase adsorbed were washed with 50 mL of K buffer (1M KCl/ 1xTNT), G buffer (30% Glycerol, 0.5MKCl/1xTNT), and aurora 2 kinase was obtained.

(0172)

(2). Aurora 2 kinase assay.

Buffer for enzyme reaction (200 mM Tris-HC1[pH7.0] 1.5 μl, 100 mM MgC12), 50 mM dithiothreitol 1.5 μl, 1 mM peptide substrate (LRRASLG) 1.5 μl, and DMSO solution of Compound 1.5 μl was added to each well.

(0173)

Aurora 2 kinase (lmg/ml) 1.5 μl diluted in enzyme diluent [50 mM Tris-HCl (pH6.8), 200 mM NaC1, 50% glycerol, 1mg/ml BSA] was added to all wells other than the "blank" well. Enzyme diluent 1.5 μl which did not contain aurora 2 kinase was added to "blank" well. DMSO solution 1.5 μl was added to "total" well.

(0174)

Next, 5 μl of 30 μM ATP solution containing 1.2 μCi [(32P)ATP (Muromachi Chemicals, specific activity >3500 Ci/mmol)] was added to every test well, and incubated at room temperature for 60 minutes, and reaction mixture 5 μl was spotted on on phosphocellulose (Wattman, p81) filter, to adsorb the 32P-labelled peptide onto the filter. Thereafter, the filter was washed three times with 0.75 % phosphoric acid solution, to eliminate the unreacted material, and reacted 32P was counted using BAS5000 (FUJIFILM company).

(0175)

Taking the count value of "blank" (without enzyme) as 0 %, and the count value of "total" (without compound) as contrast value, the IC50 value of enzyme activity was determined.

(0176)

(3). Evaluation result.

From the results of evaluation of compound according to the said (2) aurora 2 kinase assay procedure, the compound of formula (1) of this invention were observed to inhibit aurora 2 kinase activity. The results are shown in Table 2. The "compound" column shown in Table 2 respectively denotes compound number as disclosed in Table 1.

(0177)

[Table 2]

Compound	IC50 Value (nM)
26	20
44	8
45	8
46	5
54	16
108	15
119	37
120	71
135	4

(0178)

As a result the compound which was represented with Example of this invention clearly showed strong aurora 2 kinase activity inhibiting action.

Possible Applications in Industry

(0179)

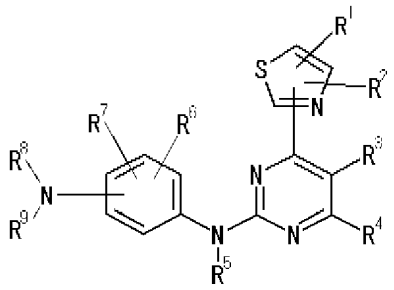
In accordance with this invention, it is possible to put forward novel aminopyrimidine compound.

(0180)

Moreover this application is based on Japan Application No. 2004-150962 dated May 20, 2004, and in included in its entirety by this citation.

Patent Claims

1. Compound represented by



(I)

[wherein, R1 and R2 are the same or different, and denote halogen atom, alkyl, hydroxy, alkoxy, amino, alkylamino or acylamino,

R3 and R4 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy or alkoxy,

R5 denotes a hydrogen atom, alkyl or acyl,

R6 and R7 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy, alkoxy, amino, alkylamino, acylamino, carbamoyl, alkylcarbamoyl, carboxy, alkoxycarbonyl, sulphamoyl, alkyl sulphamoyl, nitro or cyano,

R8 denotes COR10, CO2R10, CONR10R11, CSNR10R11, SO2R10 or OR10 [wherein, R10 and R11 are the same or different and denote -T-R12 {wherein, T may be absent or denotes 1-6C alkylene, 2-6C alkenylene, 2-6C alkynylene or one in which 1-3 methylenes in said alkylene, alkenylene, alkynylene have been replaced by C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)N(R14)-, -OC(=O)N(R14)-, -NR14-, -N(R14)O-, N(R14)C(=O)-, -N(R14)C(=O)O-, -N(R14)C(=O)N(R15)-, -S(O2)-, NR14S(O2)-, -S(O2)N(R14)-, -N(R14)C(NH)N(R15)-, oxygen atom or sulfur atom (wherein, R14 and R15 are the same or different, and denote hydrogen or alkyl), R12 denotes hydrogen, halogen atom, hydroxy, alkyl, amino, cycloalkyl, heterocycle or aryl)}, or R10 and R11 together with the nitrogen to which they are bonded denotes group forming 5-7 membered ring],

R9 denotes a hydrogen atom, alkyl, hydroxy, alkoxy or acyl, and when R8 denotes OR10, then R9 denotes a hydrogen atom;

or R8 and R9 together with the nitrogen atom to which they are bonded denote group forming 5-7 membered ring].

and medicinally permissible salt, hydrate, aqueous adduct or solvate.

2. A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with Claim 1, wherein in the aforesaid formula (1)

R3 and R4 may be the same or different and denote a hydrogen atom or alkyl,

R6 and R7 are the same or different and denote a hydrogen atom, halogen atom, alkyl, hydroxy or alkoxy,
R8 denotes COR10, CONR10R11, SO2R10 or OR10 (wherein, R10 and R11 are the same or different and denote -T-R12 {wherein, T may be absent or denotes 1-6C alkylene or the said alkylene wherein 1-3 methylenes have been replaced by C(=O)-, -C(=O)O-, -C(=O)N(R14)-, --NR14-, N(R14)C(=O)-, or oxygen atom }, or R10 and R11 together with the nitrogen to which they are bonded denotes group forming optionally substituted 5-7 membered ring which may further include heteroatom selected from oxygen atom, sulfur atom and NH},
R9 denotes a hydrogen atom, alky, or acyl,
or R8 and R9 together with the nitrogen atom to which they are bonded denote group forming 5-7 membered ring.

3. A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with Claim 1 or 2 wherein R1 and R2 in the aforesaid formula (1) are the same or different, and denote alkyl or acylamino.

4. A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of Claims 1-3 wherein R3 and R4 in the aforesaid formula (1) respectively denote hydrogen atoms.

5. Compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of Claims 1-3 wherein R5 in the aforesaid formula (1) denotes a hydrogen atom.

6. A compound, medicinally permissible salt, hydrate, aqueous adduct or solvate in accordance with any of Claims 1-5 wherein R3 and R4 in the aforesaid formula (1) respectively denote hydrogen atoms, and R5 denotes a hydrogen atom.

7. Treatment and/or prevention agent of cancer characterised by containing aminopyrimidine compound represented by Claims 1-6 or medicinally permissible salt, hydrate, aqueous adduct or solvate therof.

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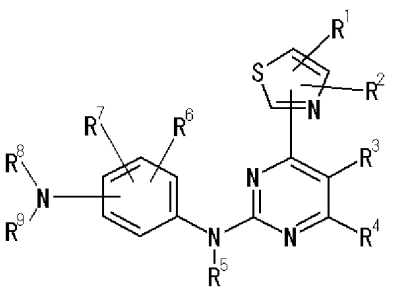
WO 2005/113550 A1

(54) Title: AMINOPYRIMIDINE DERIVATIVE AND MEDICINAL USE THEREOF

(54) 発明の名称: アミノピリミジン誘導体及びその医薬としての用途



(I)

(57) Abstract: An aminopyrimidine compound represented by the following general formula (I), pharmaceutically acceptable salt, hydrate, water adduct, and solvate. These compounds were found to potently inhibit proteinkinases, especially aurora 2 kinase, and be capable of sufficiently acting in the living body. The invention has been thus completed. [Chemical formula 1]

(57) 要約: 下記一般式（Ｉ）により表されるアミノピリミジン化合物、医薬上許容しうる塩、水和物、水付加物及び溶媒和物がプロテインキナーゼ、特に、オーロラ２キナーゼを強力に阻害しかつ生体内で十分作用しうる化合物であることを見出し、本発明を完成するに至った。【化１】

明 細 書

アミノピリミジン誘導体及びその医薬としての用途

技術分野

[0001] 本発明は、新規なアミノピリミジン化合物及びそれを有効成分とする医薬に関するものである。

背景技術

[0002] プロテインキナーゼは、細胞外の媒介物質及び環境の変化に反応して細胞の活性化、成長及び分化をコントロールするシグナル伝達に関与することが知られている。プロテインキナーゼは、一般に、そのリン酸化の基質によってセリン／スレオニンキナーゼとチロシンキナーゼの2つのグループに分類される。

[0003] プロテインキナーゼの異常な活性化は、細胞の異常増殖を伴う多数の疾患を引き起こすことが知られている。例えば、癌、腫瘍、過生、肺線維症、脈管形成、乾癬、アテローム、血管形成術後の狭窄又は再狭窄のような血管内平滑筋増殖のような過増殖障害が挙げられる。

[0004] ここで、悪性腫瘍は、癌細胞が多段階的遺伝子変化を経て細胞制御の破綻を引き起こした結果生じる。典型的な癌細胞は周りの組織を侵襲する能力及び異なる器官部位へ転移する能力に加え、異常に高度な増殖能を獲得している。細胞増殖での正常な調節の欠損は、細胞周期の進行を制御するシグナル伝達系の異常から発生することが考えられる。

[0005] 真核生物では、細胞周期は主としてタンパク質リン酸化のシグナル伝達経路によって制御されており、この制御にかかわるいくつかのプロテインキナーゼが同定されている。

[0006] これらのプロテインキナーゼの一つとしてオーロラキナーゼが挙げられる。オーロラキナーゼファミリーは現時点で少なくとも3種類の関連する蛋白質ファミリーである。オーロラキナーゼは高度に保存されたセリン／スレオニンキナーゼであり、細胞周期のM期に発現することからM期の進行に重要な酵素と考えられている。酵母やショウジョウバエ、線虫を用いたオーロラ2キナーゼ相同遺伝子の機能阻害実験からもこのキ

ナーゼファミリーのM期における重要性が示唆された(非特許文献1及び非特許文献2)。またオーロラ2キナーゼが多くの癌で過剰発現している事実(非特許文献3、非特許文献4、非特許文献5、非特許文献6及び非特許文献7)や、実験的に正常細胞でオーロラ2キナーゼを過剰発現した場合に細胞が癌化の兆候を示す事実が明らかとなった(非特許文献8)。

[0007] また、ヒト腫瘍細胞系をアンチセンスオリゴヌクレオチド処理によりオーロラ2キナーゼの発現が抑制され、細胞増殖が抑制されることが示された(特許文献1)。このことは、オーロラ2キナーゼの活性を阻害することは細胞の異常増殖を抑制することが可能であり、癌をはじめとする細胞の異常増殖を伴う多数の疾患の治療に有用であると考えられる。

[0008] オーロラ2キナーゼを阻害する低分子は特許等でいくつか報告されている。例えば、特許文献2、特許文献3、特許文献4、特許文献5及び非特許文献9が挙げられる。

[0009] また、4位にチアゾール環を有するアミノピリジン化合物は以下の特許等で報告がある。例えば、特許文献6、特許文献7、特許文献8、特許文献9、特許文献10及び非特許文献10が挙げられるが、これらにオーロラ2キナーゼ阻害活性に関する記載はない。

特許文献1:特開2002－95479号公報

特許文献2:WO2001－21595号公報

特許文献3:WO2002－22601号公報

特許文献4:WO2002－96905号公報

特許文献5:WO2004－5283号公報

特許文献6:WO1997－19065号公報

特許文献7:WO2001－72745号公報

特許文献8:WO2002－46170号公報

特許文献9:WO2003－11838号公報

特許文献10:WO2003－29249号公報

非特許文献1:David M. Gloverら、Cell、81巻95～105項1995年

非特許文献2:Daniela Berdnikら、Current Biology、12巻640～647項2002年

非特許文献3:Hongyi Zhouら、Nature Genetics、20巻189～193項1998年
非特許文献4:Takuji Tanakaら、Cancer Research、59巻2041～2044項1999年
非特許文献5:C. Sakakuraら、British Journal of Cancer、84巻824～831項2001年
非特許文献6:Subrata Senら、Journal of the National Cancer Institute、94巻1320～1329項2002年
非特許文献7:Donghui Liら、Clinical Cancer Research、9巻991～997項2003年
非特許文献8:James R. Bischoffら、EMBO Journal、17巻3052～3065項1998年
非特許文献9:Elizabeth A. Harringtonら、Nature Medicine Advanced Online Publication、2004年2月22日号
非特許文献10:Shudong Wangら、Jounal of Medicinal Chemistry、47巻1662～1675項2004年

発明の開示

発明が解決しようとする課題

[0010] オーロラ2キナーゼを阻害する物質はいくつか報告があるが、未だ疾患の治療に十分な生物活性を有するものは見つかっていない。 本発明の課題は、癌をはじめとする細胞増殖性疾患の治療に有用なオーロラ2キナーゼ阻害剤を提供することにある。

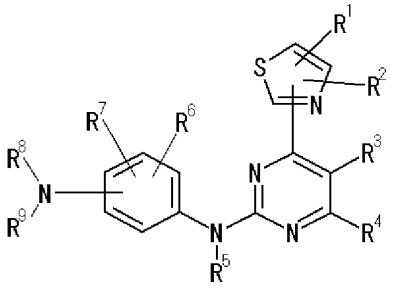
課題を解決するための手段

[0011] 本発明はかかる状況を鑑み鋭意研究を重ねた結果、下記一般式(I)により表されるアミノピリミジン化合物、医薬上許容しうる塩、水和物、水付加物及び溶媒和物がプロテインキナーゼ、特に、オーロラ2キナーゼを強力に阻害しかつ生体内で十分作用しうる化合物であることを見出し本発明を完成するに至った。

[0012] 即ち、本発明の要旨は以下の通りである。

(1)下記式(I)

[0013] [化1]



(I)

[0014] [式中、R^1及びR^2は、同一又は異なってハロゲン原子、アルキル、ヒドロキシ、アルコシキ、アミノ、アルキルアミノ又はアシルアミノを示し、

R^3及びR^4は同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ又はアルコキシを示し、

R^5は水素原子、アルキル又はアシルを示し、

R^6及びR^7は、同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ、アルコキシ、アミノ、アルキルアミノ、アシルアミノ、カルバモイル、アルキルカルバモイル、カルボキシ、アルコキシカルボニル、スルファモイル、アルキルスルファモイル、ニトロ又はシアノを示し、

R^8はCOR^{10}、CO_2R^{10}、$CONR^{10}R^{11}$、$CSNR^{10}R^{11}$、SO_2R^{10}又はOR^{10}を示し[式中、R^{10}及びR^{11}は、同一又は異なって－T－R^{12}{式中、Tは、存在しないか、C_{1-6}のアルキレン、C_{2-6}のアルケニレン、C_{2-6}のアルキニレン又はそのアルキレン、アルケニレン、アルキニレンのうち1から3個のメチレンを－C(＝O)－、－C(＝O)O－、－OC(＝O)－、－C(＝O)N(R^{14})－、－OC(＝O)N(R^{14})－、－NR^{14}－、－N(R^{14})O－、N(R^{14})C(＝O)－、－N(R^{14})C(＝O)O－、－N(R^{14})C(＝O)N(R^{15})－、－S(O_2)－、NR^{14}S(O_2)－、－S(O_2)N(R^{14})－、－N(R^{14})C(NH)N(R^{15})－、酸素原子又は硫黄原子で置換したもののいずれかを示し(式中、R^{14}及びR^{15}は、同一又は異なって水素又はアルキルを示す。)、R^{12}は水素、ハロゲン原子、ヒドロキシ、アルキル、アミノ、シクロアルキル、複素環又はアリールを示す。}又はR^{10}とR^{11}が相互に結合する窒素原子とともに5から7員環を形成する基を示す。]、

R^9は水素原子、アルキル、ヒドロキシ、アルコキシ又はアシルを示すが、R^8がOR^{10}を示す場合は、R^9は水素原子を示し、又は、

R^8及びR^9は、相互に結合する窒素原子とともに5から7員環を形成する基を示す。]で表される化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(2)上記式(I)中、R^3及びR^4は、同一又は異なって水素原子又はアルキルを示し、

R^6及びR^7は、同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ又はアルコキシを示し、

R^8はCOR^{10}、$CONR^{10}R^{11}$、SO_2R^{10}又はOR^{10}示し[式中、R^{10}及びR^{11}は、同一又は異なって－T－R^{12}{式中、Tは、存在しないか、C_{1-6}のアルキレン又はそのアルキレンのうち1から3個のメチレンを－C(＝O)－、－C(＝O)O－、－C(＝O)N(R^{14})－、－N(R^{14})－、－N(R^{14})C(＝O)－又は酸素原子で置換したもののいずれかを示す。}又はR^{10}とR^{11}が相互に結合する窒素原子とともに、さらに、酸素原子、硫黄原子及びNHから選ばれるヘテロ原子を含んでいてもよく、置換基を有していてもよい5から7員環を形成する基を示す。]、

R^9は水素原子、アルキル又はアシルを示すか、又は、

R^8及びR^9は、相互に結合する窒素原子とともに5から7員環を形成する基を示す上記(1)に記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(3)上記式(I)中、R^1及びR^2が同一又は異なって、アルキル又はアシルアミノを示す上記(1)又は(2)に記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(4)上記式(I)中、R^3及びR^4がそれぞれ水素原子を示す上記(1)から(3)のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(5)上記式(I)中、R^5が水素原子を示す上記(1)から(3)のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(6)上記式(I)中、R^3及びR^4がそれぞれ水素原子を示し、R^5が水素原子を示す上記(1)から(5)のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

(7)上記(1)から(6)で表されるアミノピリミジン化合物又はその医薬上許容される塩、水和物、水付加物及び溶媒和物を含有することを特徴とする癌の予防及び／又は治療剤。

発明の効果

[0015] 本発明によれば、上記一般式(I)で表わされるアミノピリミジン化合物、医薬上許容しうる塩、水和物、水付加物及び溶媒和物からなる群から選ばれる物質を有効成分として含む癌治療薬を提供することができる。

発明を実施するための最良の形態

[0016] 以下、本発明を詳細に説明する。

[0017] 本発明の上記一般式(I)で表される各置換基を以下に定義する。

[0018] R^1又はR^2で示される「ハロゲン原子」としては、例えばフッ素原子、塩素原子、臭素原子、ヨウ素原子等が挙げられる。

[0019] R^1又はR^2で示される「アルキル」としては、C_{1-6}のアルキル(例、メチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、sec－ブチル、tert－ブチル、ペンチル、ヘキシル等)が挙げられ、C_{1-3}のアルキル(例、メチル、エチル、プロピル、イソプロピル)が好ましく、特にメチルが好ましい。

[0020] R^1又はR^2で示される「アルコキシ」としては、例えばC_{1-6}のアルコキシが挙げられ、具体的にはメトキシ、エトキシ、プロポキシ、イソプロポキシ、ブトキシ、第3級ブトキシ等が挙げられ、好ましくはメトキシが挙げられる。

[0021] R^1又はR^2で示される「アルキルアミノ」としては、例えばC_{1-6}のアルキルアミノが挙げられ、具体的にはメチルアミノ、エチルアミノ、n－プロピルアミノ、イソプロピルアミノ、n－ブチルアミノ、ジメチルアミノ、ジエチルアミノ、N－メチル－N－エチルアミノ、ピロリジン-1-イル、ピペリジン-1-イルが挙げられ、好ましくはメチルアミノ、ジメチルアミノが挙げられる。

[0022] R^1又はR^2で示される「アシルアミノ」としては、例えばC_{1-6}のアシルアミノが挙げられ、具体的にはホルミルアミノ、アセチルアミノ、プロピオニルアミノ、ブチリルアミノが挙げられ、好ましくはアセチルアミノが挙げられる。

[0023] R^1又はR^2で示されるアルキル、アルコキシ、アルキルアミノ又はアシルアミノは、置換基を有していてもよい。ここで、置換基としては、例えば、C_{1-6}のアルキル(例、メチル、エチル等)、ハロゲン原子(例、フッ素原子、塩素原子、臭素原子、ヨウ素原子等)、ヒドロキシ、C_{1-6}のアルコキシ、オキソ、カルボキシ、C_{1-6}のアルコキシカルボニル

（例、tert−ブトキシカルボニル等）、アシル(例、ホルミル等)、アシルオキシ、アミノ、アルキルアミノ、ジアルキルアミノ、アミド、アルキルアミド、カルバモイル、スルファニル、アルキルスルファニル、スルフィノ、アルキルスルホニル（例、メチルスルホニル、エチルスルホニル等）、スルファモイル、アルキルスルファモイル等が挙げられる。

[0024] R^3又はR^4で示される「ハロゲン原子」としては、前記R^1又はR^2で示される「ハロゲン原子」と同様のものが挙げられる。

[0025] R^3又はR^4で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられ、好ましくはメチルが挙げられる。

[0026] R^3又はR^4で示される「アルコキシ」としては、前記R^1又はR^2で示される「アルコキシ」と同様のものが挙げられる。

[0027] R^3又はR^4で示される、アルキル又はアルコキシは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

[0028] R^5で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられ、好ましくはメチルが挙げられる。

[0029] R^5で示される「アシル」としては、例えば炭素数が1から6のアシルが挙げられ、具体的にはホルミル、アセチル、プロピオニル、２－メチルプロピオニル、ブチリル等が挙げられ、好ましくはアセチルが挙げられる。

[0030] R^5で示される、アルキル又はアシルは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

[0031] R^6及びR^7で示される「ハロゲン原子」としては、前記R^1又はR^2で示される「ハロゲン原子」と同様のものが挙げられ、好ましくは塩素原子が挙げられる。

[0032] R^6及びR^7で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられ、好ましくはメチルが挙げられる。

[0033] R^6及びR^7で示される「アルコキシ」としては、前記R^1又はR^2で示される「アルコキシ」と同様のものが挙げられ、好ましくはメトキシが挙げられる。

[0034] R^6及びR^7で示される「アルキルアミノ」としては、前記R^1又はR^2で示される「アルキルアミノ」と同様のものが挙げられ、好ましくはメチルアミノ、ジメチルアミノが挙げられる。

[0035] R^6及びR^7で示される「アシルアミノ」としては、前記R^1又はR^2で示される「アシルアミノ」と同様のものが挙げられる。

[0036] R^6及びR^7で示される「アルキルカルバモイル」としては、例えばC_{1-6}のアルキルカルバモイルが挙げられ、具体的には、メチルカルバモイル、エチルカルバモイル、ジメチルカルバモイル、エチルメチルカルバモイル等が挙げられる。

[0037] R^6及びR^7で示される「アルコキシカルボニル」としては、例えばC_{1-6}のアルコキシカルボニルが挙げられ、具体的にはメトキシカルボニル、エトキシカルボニル、プロポキシカルボニル、イソプロポキシカルボニル、ブトキシカルボニル、第3級ブトキシカルボニル等が挙げられる。

[0038] R^6及びR^7で示される「アルキルスルファモイル」としては、例えばC_{1-6}のアルキルスルファモイルが挙げられ、具体的にはメチルスルファモイル、エチルスルファモイル等が挙げられる。

[0039] R^6又はR^7で示される、アルキル、アルコキシ、アルキルアミノ、アシルアミノ、アルキルカルバモイル、アルコキシカルボニル又はアルキルスルファモイルは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

[0040] R^9で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられ、好ましくはメチルが挙げられる。

[0041] R^9で示される「アルコキシ」としては、前記R^1又はR^2で示される「アルコキシ」と同様のものが挙げられる。

[0042] R^9で示される「アシル」としては、前記R^4で示される「アシル」と同様のものが挙げられ、好ましくはアセチル、ブチリル及びベンゾイルが挙げられる。

[0043] R^9で示される、アルキル、アルコキシ又はアシルは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

[0044] R^8及びR^9が、相互に結合する窒素原子とともに5から7員環を形成する基としては、5から7員環中、酸素原子、硫黄原子及びN－R^{13}(R^{13}は水素原子、アルキル、アラルキル又はアシルを示す。)から選ばれるヘテロ原子を含んでいてもよい。5ないし7員環としては、例えば、ピロリジン、ピペリジン、ピペラジン、モルホリン、チオモルホリ

ン、チオフェン、フラン、ピロール、イミダゾール、ピラゾール、ピリジン、ピラジン、ピリミジン、チアゾール、イソオキサゾールが挙げられる。また、5から7員環は、置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられ、その他にも酸素原子などが挙げられる。

[0045] R^{10}及びR^{11}が、相互に結合する窒素原子とともに5から7員環を形成する基としては、5から7員環中、酸素原子、硫黄原子及び窒素原子から選ばれるヘテロ原子を含んでいてもよい。5ないし7員環としては、例えば、ピロリジン、ピペリジン、ピペラジン、モルホリン、チオモルホリン、チオフェン、フラン、ピロール、イミダゾール、ピラゾール、ピリジン、ピラジン、ピリミジン、チアゾール、イソオキサゾールが挙げられる。また、5から7員環は、置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

[0046] R^{12}で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられるが、好ましくはC_{1-4}のアルキルが挙げられ、具体的にはメチル、エチル、イソプロピル、tert-ブチル、トリフルオロエチルが挙げられる。

[0047] R^{12}で示される「ハロゲン原子」としては、前記R^1又はR^2で示される「ハロゲン原子」と同様のものが挙げられ、好ましくは塩素原子と臭素原子が挙げられる。

[0048] R^{12}で示される「シクロアルキル」としては、例えばC_{3-8}のシクロアルキルが挙げられ、具体的にはシクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル等が挙げられ、好ましくはシクロプロピル、シクロヘキシルが挙げられる。

[0049] R^{12}で示される「複素環」としては、例えば、炭素原子以外に、窒素原子、硫黄原子及び酸素原子から選ばれる1又は2種のヘテロ原子を1ないし4個含んでいてもよい5ないし7員芳香族複素環又は非芳香族複素環が挙げられ、具体的にはピロリジン、ピペリジン、ピペラジン、モルホリン、チオモルホリン、チオフェン、フラン、ピロール、イミダゾール、ピラゾール、ピリジン、ピラジン、ピリミジン、チアゾール、イソオキサゾールが挙げられ、好ましくはピペラジン、ピペリジン、モルホリン、ホモピペラジン、チオフェン、ピリジン、チアゾールが挙げられる。

[0050] R^{12}で示される「アリール」としては、単環又は縮合環が挙げられ、例えばフェニル、1－ナフチル、2-ナフチル等が挙げられ、好ましくはフェニルが挙げられる。

[0051] R^{12}で示されるアルキル、アミノ、シクロアルキル、複素環又はアリールは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられ、その他にも複素環（例、4−メチルピペラジノメチル、モルホリノメチル等）等が挙げられる。

[0052] R^{13}で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられる。

[0053] R^{13}で示される「アラルキル」としては、例えばC_{7-16}のアラルキルが挙げられ、具体的にはベンジル、フェネチル、ジフェニルメチル、１－ナフチルメチル等が挙げられる。

[0054] R^{13}で示される「アシル」としては、前記R^4で示される「アシル」と同様のものが挙げられる。

[0055] R^{13}で示される、アルキル、アラルキル又はアシルは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

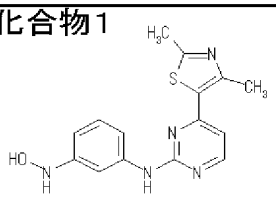
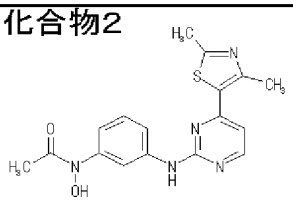
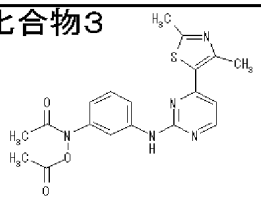
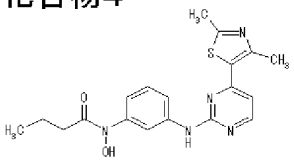
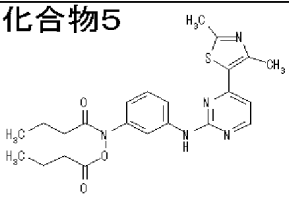
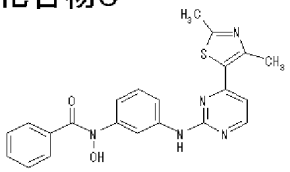
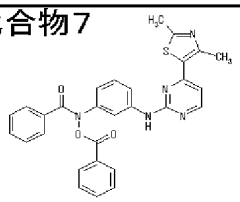
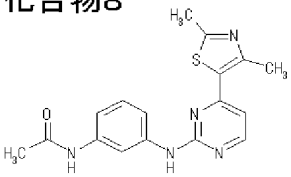
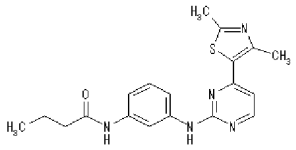
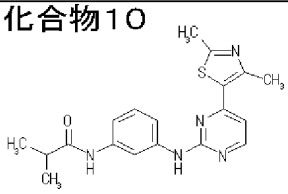
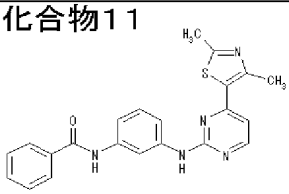
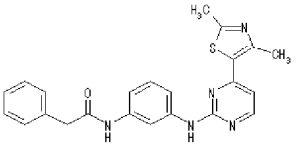
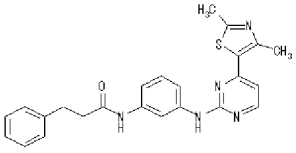
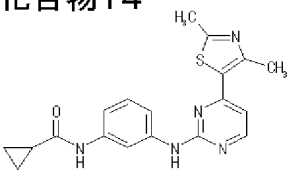
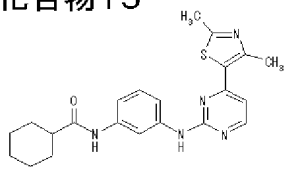
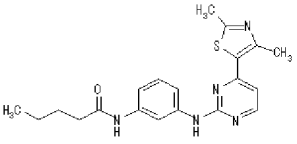
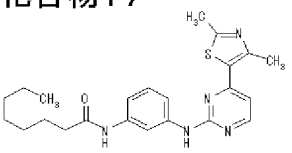
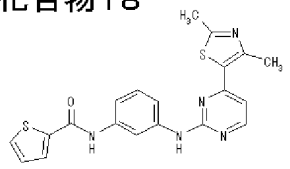
[0056] R^{14}及びR^{15}で示される「アルキル」としては、前記R^1又はR^2で示される「アルキル」と同様のものが挙げられる。

[0057] R^{14}及びR^{15}で示されるアルキルは置換基を有していてもよい。ここで、置換基としては、前記R^1又はR^2で示される置換基と同様のものが挙げられる。

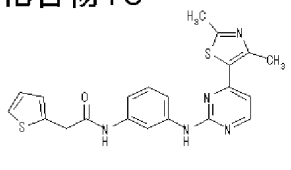
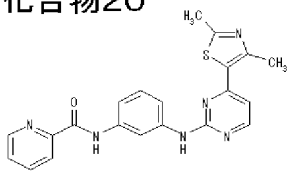
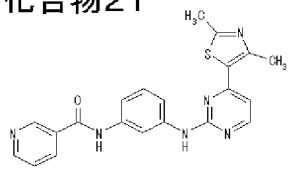
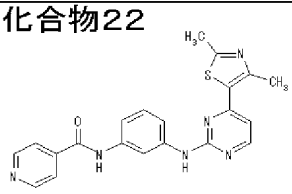
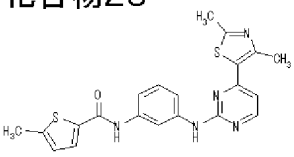
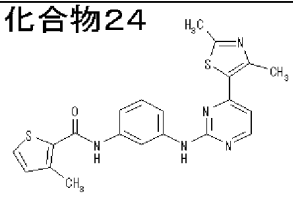
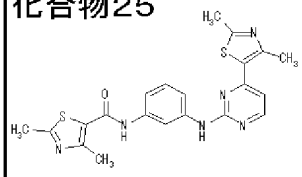
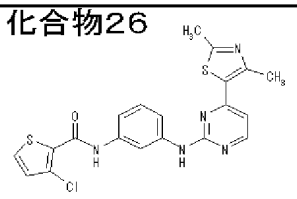
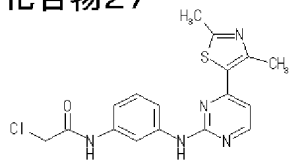
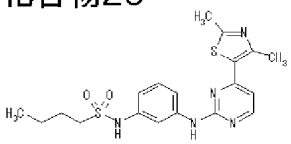
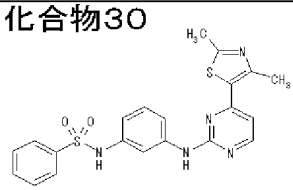
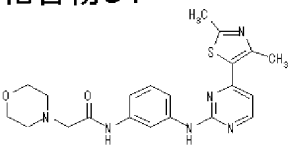
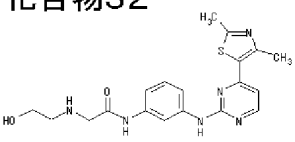
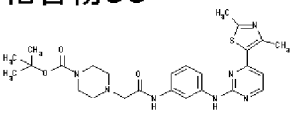
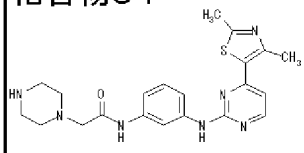
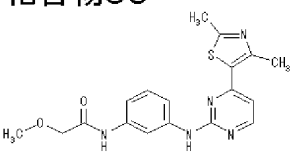
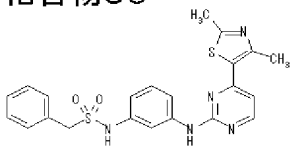
[0058] 本発明化合物の具体例として、例えば以下の化合物が挙げられる。

[0059] 表1

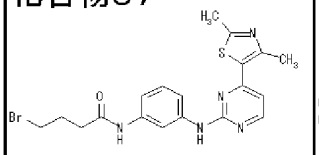
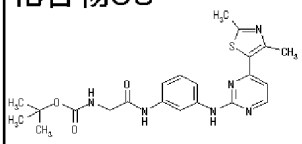
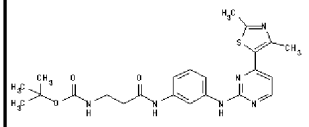
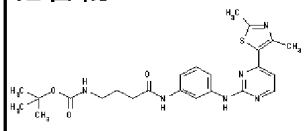
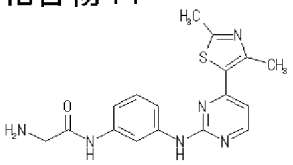
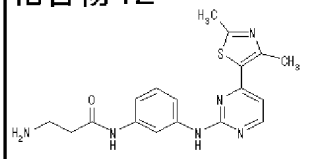
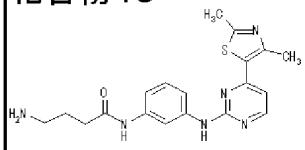
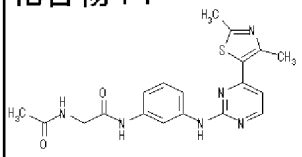
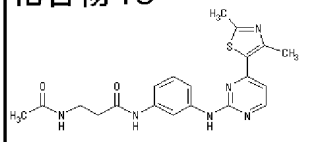
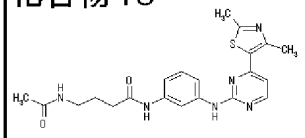
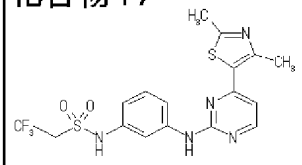
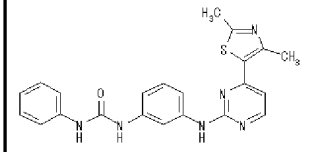
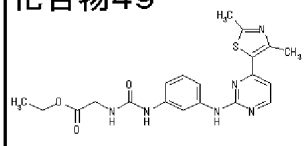
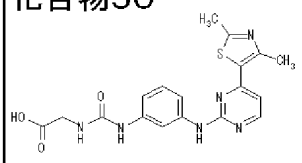
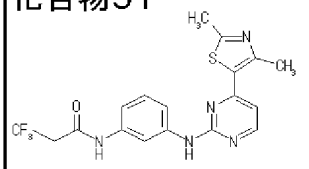
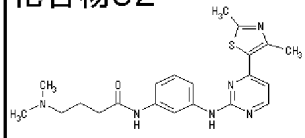
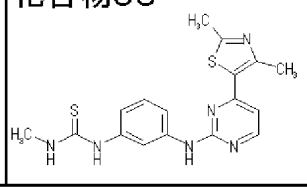
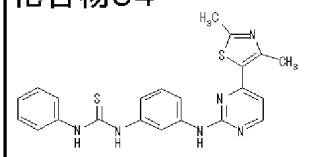
[0060] [化2]

化合物1 	化合物2 	化合物3 
化合物4 	化合物5 	化合物6 
化合物7 	化合物8 	化合物9 
化合物10 	化合物11 	化合物12 
化合物13 	化合物14 	化合物15 
化合物16 	化合物17 	化合物18 

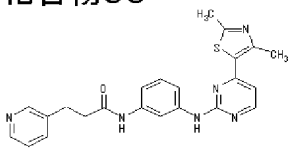
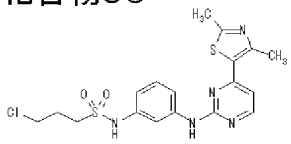
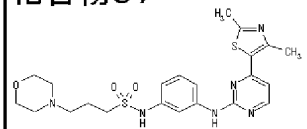
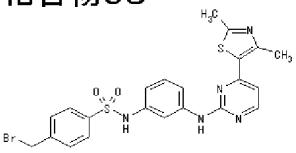
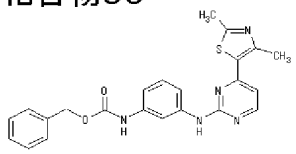
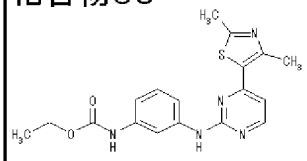
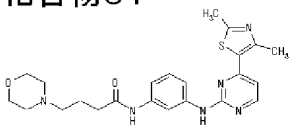
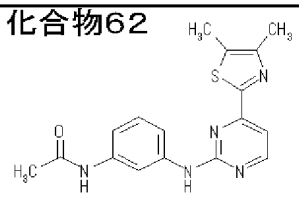
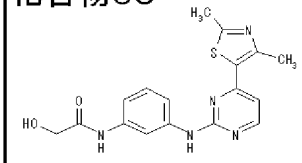
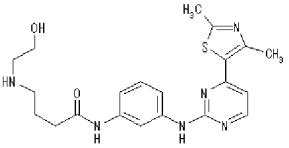
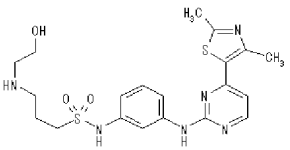
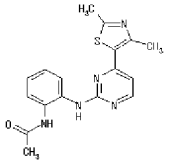
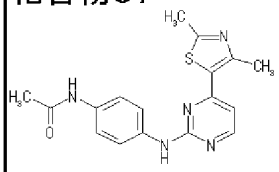
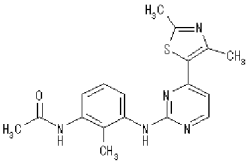
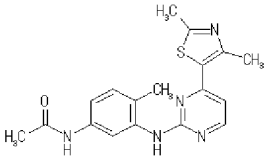
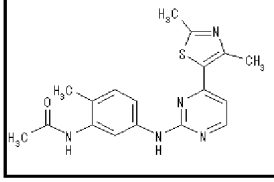
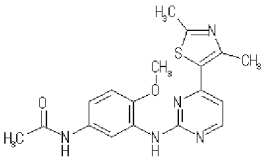
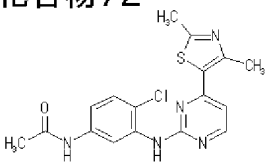
[0061] [化3]

化合物19 	化合物20 	化合物21 
化合物22 	化合物23 	化合物24 
化合物25 	化合物26 	化合物27 
化合物28 	化合物29 	化合物30 
化合物31 	化合物32 	化合物33 
化合物34 	化合物35 	化合物36 

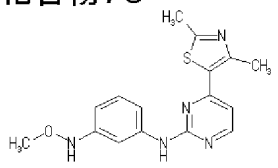
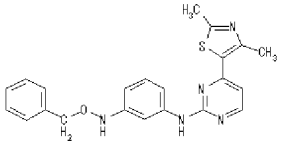
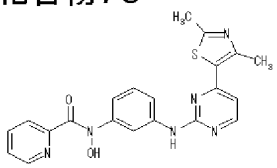
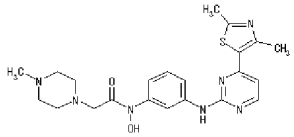
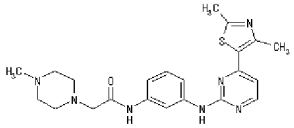
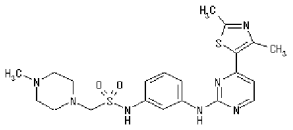
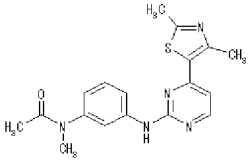
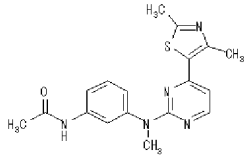
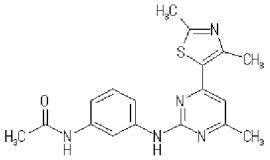
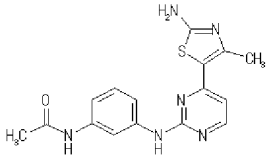
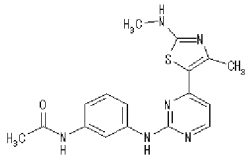
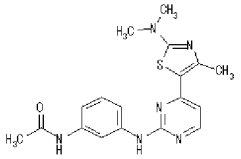
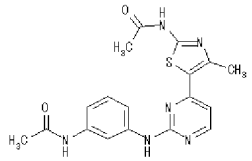
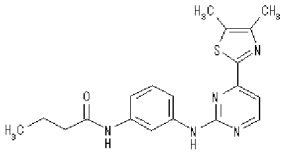
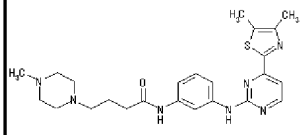
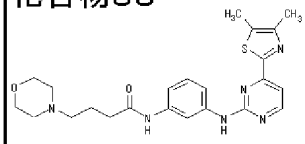
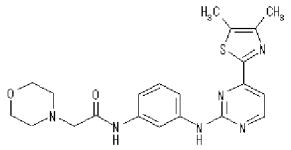
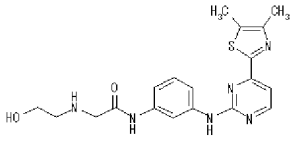
[0062] [化4]

化合物37 	化合物38 	化合物39 
化合物40 	化合物41 	化合物42 
化合物43 	化合物44 	化合物45 
化合物46 	化合物47 	化合物48 
化合物49 	化合物50 	化合物51 
化合物52 	化合物53 	化合物54 

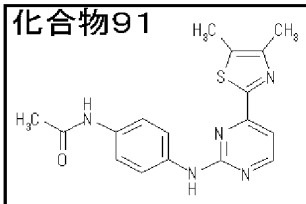
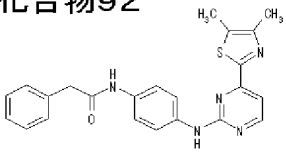
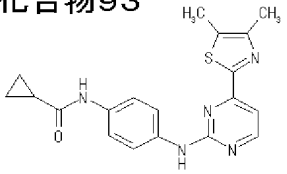
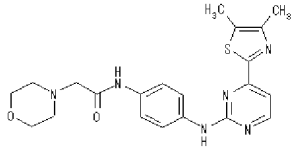
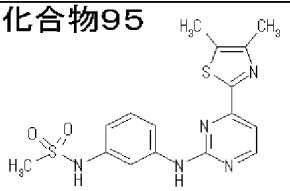
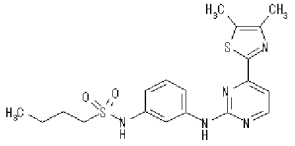
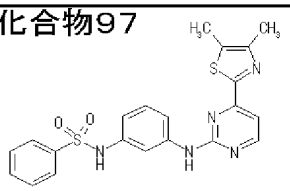
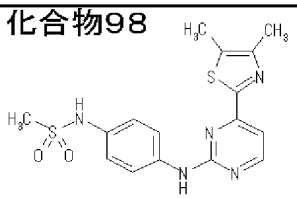
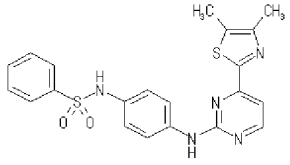
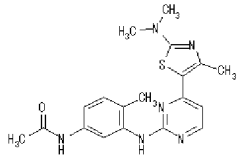
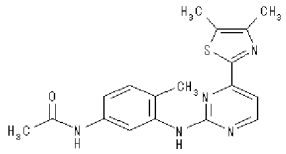
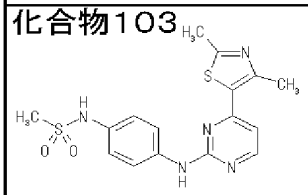
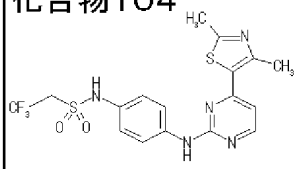
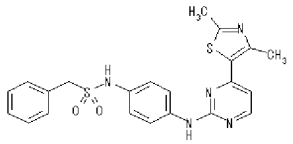
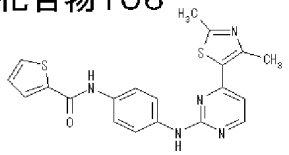
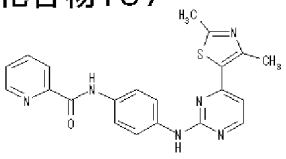
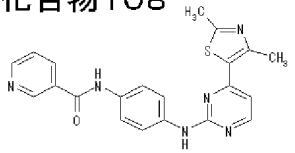
[0063] [化5]

化合物55 	化合物56 	化合物57 
化合物58 	化合物59 	化合物60 
化合物61 	化合物62 	化合物63 
化合物64 	化合物65 	化合物66 
化合物67 	化合物68 	化合物69 
化合物70 	化合物71 	化合物72 

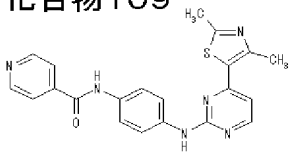
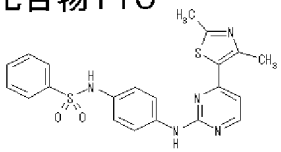
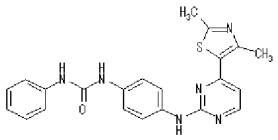
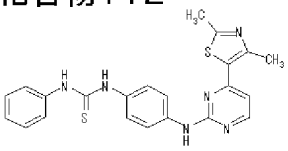
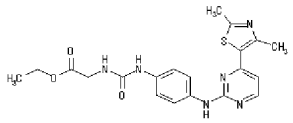
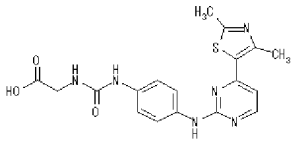
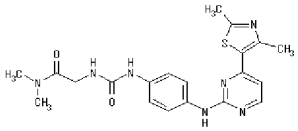
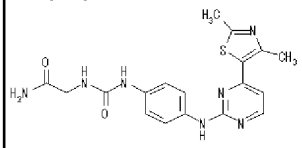
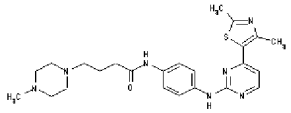
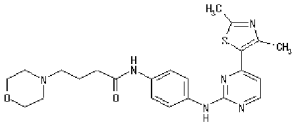
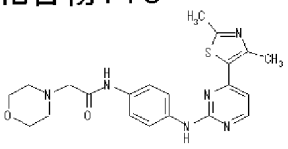
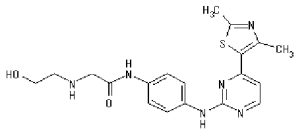
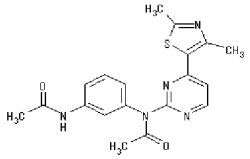
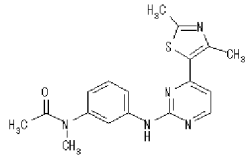
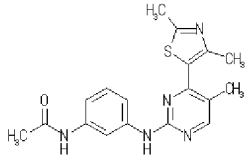
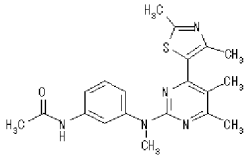
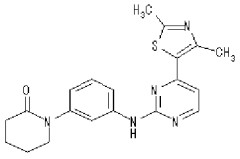
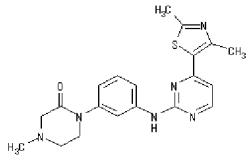
[0064] [化6]

化合物73 	化合物74 	化合物75 
化合物76 	化合物77 	化合物78 
化合物79 	化合物80 	化合物81 
化合物82 	化合物83 	化合物84 
化合物85 	化合物86 	化合物87 
化合物88 	化合物89 	化合物90 

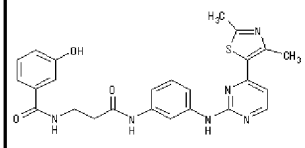
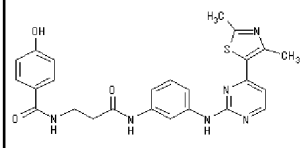
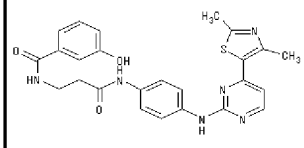
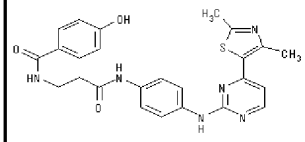
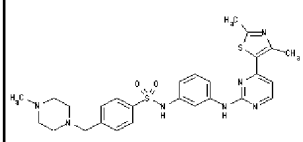
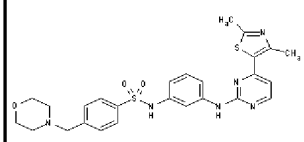
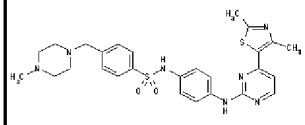
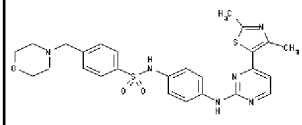
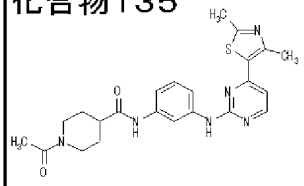
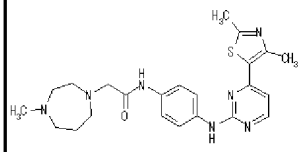
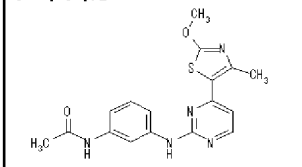
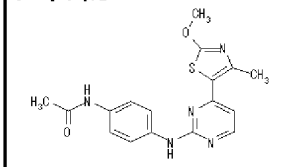
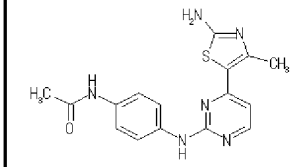
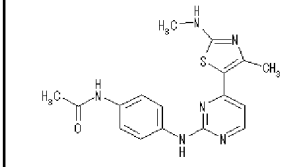
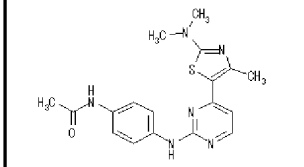
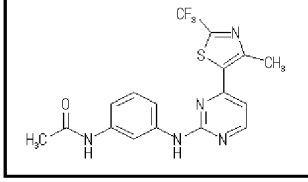
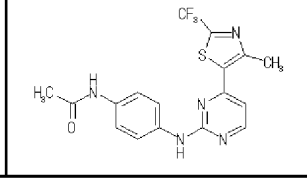
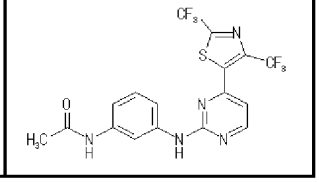
[0065] [化7]

化合物91 	化合物92 	化合物93 
化合物94 	化合物95 	化合物96 
化合物97 	化合物98 	化合物99 
化合物100 	化合物101 	化合物102 
化合物103 	化合物104 	化合物105 
化合物106 	化合物107 	化合物108 

[0066] [化8]

化合物109 	化合物110 	化合物111 
化合物112 	化合物113 	化合物114 
化合物115 	化合物116 	化合物117 
化合物118 	化合物119 	化合物120 
化合物121 	化合物122 	化合物123 
化合物124 	化合物125 	化合物126 

[0067] [化9]

化合物127 	化合物128 	化合物129 
化合物130 	化合物131 	化合物132 
化合物133 	化合物134 	化合物135 
化合物136 	化合物137 	化合物138 
化合物139 	化合物140 	化合物141 
化合物142 	化合物143 	化合物144 

[0068] 本発明の一般式(I)の化合物における医薬上許容しうる塩としては無機酸又は有機酸との酸付加塩が挙げられる。

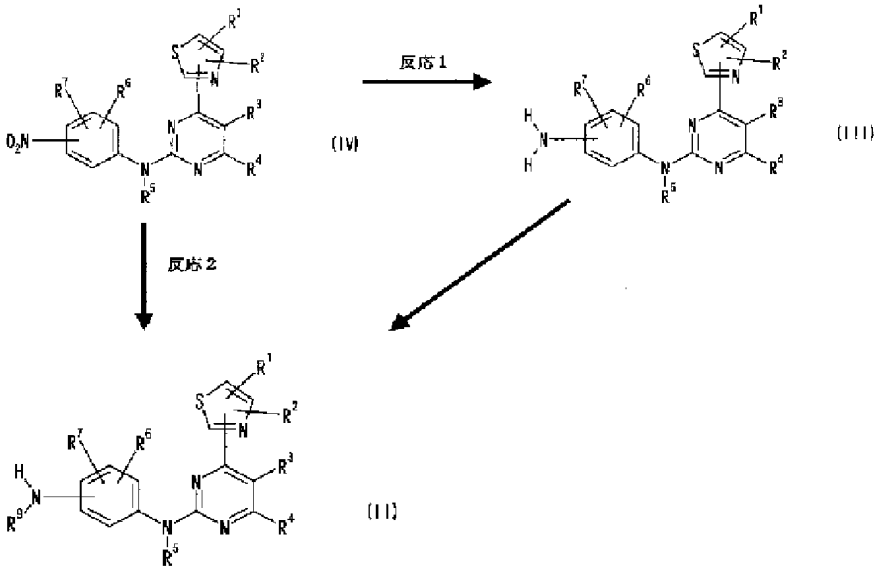
[0069] また、本発明の化合物は、水付加物、水和物及び溶媒和物として存在することもあるので、これらの水付加物、水和物及び溶媒和物もまた本発明に包含される。

[0070] 本発明の一般式(I)の化合物は、以下に述べる方法により製造できる。

[0071] 下記一般式の式中、特に示さない限り、R^1、R^2、R^3、R^4、R^5、R^6、R^7又はR^9は前記

の通りである。

[0072] [化10]



[0073] 1．反応1

上記一般式(IV)(Shudong Wangら、Jounal of Medicinal Chemistry、47巻1662～1675項2004年)で表される化合物を、適当な還元条件下、すなわち、鉄などの触媒の存在下で、適当な酸(例えば、酢酸または塩酸など)と適当な溶媒(例えば、エタノール、ジオキサン、水又はこれらの任意の混合溶媒など)中、60℃から100℃の条件下で、0．5時間から6時間反応させることにより、上記一般式(III)の化合物を製造することができる。

[0074] 上記一般式(III)で表される化合物を$X-R^{9'}$(式中、$R^{9'}$は前記定義のR^9から水素原子、ヒドロキシ又はアルコキシ基を除いた基を表し、Xはハロゲン原子又は良好な脱離基を示す)と反応させることにより、上記一般式(II)(式中、R^9が水素原子、ヒドロキシ又はアルコキシ以外を示す)で表される化合物を製造することができる。

[0075] また、上記一般式(III)で表される化合物と$R^{16}-CO-R^{17}$(式中、R^{16}及びR^{17}は、同一又は異なって適当な置換基を有していてもよいアルキル基、又は、一方が水素原子を示す)を反応させた後、水素を添加することにより、上記一般式(II)(式中、R^9が水素原子、ヒドロキシ又はアルコキシ以外を示す)で表される化合物を製造することができる。

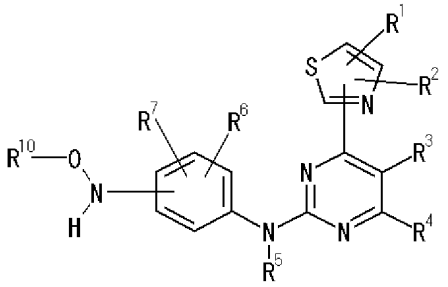
2. 反応2

上記一般式(IV)で表される化合物をパラジウム－炭素(Pd－C)の存在下で、水素添加反応を行い、適当な溶媒(例えば、メタノール、エタノール、水又はこれらの任意の混合溶媒など)中、室温条件下で1時間から12時間反応させることにより、上記一般式(II)(式中、R^9が水素原子、ヒドロキシ又はアルコキシを示す)で表される化合物を製造することができる。

[0076] さらに、上記一般式(II)で表される化合物を、X－COR^{10}、X－CO_2R^{10}、R^{10}－NCO、R^{10}－NCS又はX－SO_2R^{10}(R^{10}は前記の通りであり、Xはハロゲン原子、ヒドロキシ又は良好な脱離基を示す。)のいずれかの化合物を反応させることにより、あるいは場合によってはさらに一般に用いられるアルキル化剤を用いて反応させることにより、一般式(I)で表される化合物(式中、R^8がCOR^{10}、CO_2R^{10}、$CONR^{10}R^{11}$、$CSNR^{10}R^{11}$又はSO_2R^{10}を示す)を製造することができる。

[0077] その他、上記一般式(IV)で表される化合物をパラジウム－炭素(Pd－C)の存在下で、水素添加反応を行い、適当な溶媒(例えば、エタノール、エタノール、水又はこれらの任意の混合溶媒など)中、室温条件下で1時間から12時間反応させることにより、一般式(I)中、R^8がOR^{10}を示すような下記一般式(Ia)

[0078] [化11]



(Ia)

[0079] (式中、R^1、R^2、R^3、R^4、R^5、R^6、R^7又はR^{10}は前記の通りである)で表される化合物を製造することができる。

[0080] さらに、上記の各合成過程において適用可能な場合には、それぞれの化合物を誘導化し、当該分野に周知の方法を用いて他の化合物に変換することができる。

[0081] 上記の各合成過程では、官能基の保護又は脱保護が時々必要である。適当な保護基は官能基のタイプによって選択でき、当該分野に周知の方法を適用してもよい。

[0082] 一般式(I)で表わされるシアノピリジン誘導体の塩、又はそれらの水和物若しくは溶媒和物は、シアノピリジン誘導体から公知の方法により製造することができる。

[0083] 上記方法にて得られる一般式(I)の化合物、又はその医薬上許容しうる塩、水付加物、水和物及び溶媒和物は強力なオーロラ2キナーゼ阻害作用を有し、癌予防及び／又は治療薬として有用である。

[0084] 本発明の化合物を医薬として用いる場合の投与方法は当業者が適宜選択可能である。例えば、皮下注射、静脈内注射、筋肉注射、腹腔内注射等の非経口投与、又は経口投与のいずれの投与経路を選択することも可能である。投与量は患者の年齢、健康状態、体重等の条件、同時に投与される医薬がある場合にはその種類や投与頻度等の条件、あるいは所望の効果の性質等により適宜決定することができる。一般的には、有効成分の1日投与量は0．5～300mg／kg体重、通常1～30mg／kg体重であり、一日あたり1回あるいはそれ以上に分けて投与することができる。

[0085] また、本発明の化合物を医薬として用いる場合には、上記の有効成分と1種又は2種以上の製剤用添加物とを含む医薬組成物を調製して投与することが好ましい。

[0086] 経口投与に適した医薬組成物としては、例えば、錠剤、カプセル剤、粉剤、液剤、エリキシル剤等を挙げることができ、非経口投与に適した医薬組成物としては、例えば、液剤あるいは懸濁化剤等の殺菌した液状の形態の医薬組成物を例示することができる。

[0087] 医薬組成物の調製に用いられる製剤用添加物の種類は特に制限されず、種々医薬組成物の形態に応じて適宜の製剤用添加物を選択することが可能である。製剤用添加物は固体又は液体のいずれであってもよく、例えば固体担体や液状担体等を用いることができる。 固体担体の例としては通常のゼラチンタイプのカプセルを用いることができる。また、例えば、有効成分を1種又は2種以上の製剤用添加物とともに、あるいは製剤用添加物を用いずに錠剤化することができ、あるいは粉末として調製して包装することができる。これらのカプセル、錠剤、粉末は、一般的には製剤の全重量に対して5～95重量%、好ましくは5～90重量%の有効成分を含むことができ、投与単位形態は5～500mg、好ましくは25～250mgの有効成分を含有するのがよい。液状担体としては水、あるいは石油、ピーナツ油、大豆油、ミネラル油、ゴマ油等

の動植物起源の油又は合成の油が用いられる。

[0088] また、一般に生理食塩水、デキストロールあるいは類似のショ糖溶液、エチレングリコール、プロピレングリコール、ポリエチレングリコール等のグリコール類が液状担体として好ましく、特に生理食塩水を用いた注射液の場合には通常0．5～20％、好ましくは1～10％重量の有効成分を含むように調製することができる。

実施例

[0089] 以下、本発明を製造例、実施例及び薬理実験例によりさらに具体的に説明するが、本発明は、これらの記載に限定されるものではない。なお、1H－NMRは特に言及しない限りDMSO－d6を溶媒とし300MHz又は400MHzで測定した。1H－NMRのケミカルシフト値は、内部標準としてテトラメチルシラン（TMS）を用い、相対的なデルタ（δ）値をパーツパーミリオン（ppm）で表した。カップリング定数は自明な多重度をヘルツ（Hz）で示し、s（シングレット）、d（ダブレット）、t（トリプレット）、q（カルテット）、m（マルチプレット）、dd（ダブルダブレット）、brs（ブロードシングレット）等と表記した。カラムクロマトグラフィーはメルク社製又は富士シリシア化学製のシリカゲルを用いて行った。

[0090] 製造例1 3－ニトロフェニルグアニジン

3－ニトロアニリン(20.0g、0.15mol)及びシアナミド（10.7g）の1，4－ジオキサン（150ml）溶液に氷冷下4N塩酸／1，4－ジオキサン溶液（63ml）を加え、80℃で4時間撹拌した。反応液に氷冷下6N水酸化ナトリウム水溶液（50.7ml）を加えた後、減圧下1，4－ジオキサンを留去した。析出した沈殿をろ取、水洗し、減圧下60℃で乾燥することにより3－ニトロフェニルグアニジン（23.8g、91%）で得た。

1H-NMR: 7.60(1H, m), 7.52(1H, brs), 7.39(1H, dd, 8Hz, 8Hz), 7.16(1H, d, J=8Hz), 5.41(4H, brs)。

[0091] 製造例2 3－ジメチルアミノ－1－（2，4－ジメチルチアゾール－5－イル）プロペノン

5－アセチル－2，4－ジメチルチアゾール（20.0g、0.13mol）をエタノール（85ml）に溶解し、N，N－ジメチルホルムアミドジメチルアセタール（85.6ml）を加え4時間加熱還流した。反応液を減圧下濃縮し、残渣にジエチルエーテルを加え析出した結晶を

ろ取することにより3－ジメチルアミノ－1－(2, 4－ジメチルチアゾール－5－イル)プロペノン(18.9g、70%)を得た。

1H-NMR: 7.64(1H, d, J=12Hz), 5.32(1H, d, J=12Hz), 3.13(3H, brs), 2.58(3H, brs), 2.58(3H, s), 2.55(3H, s)。

[0092] 製造例3 (4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)－(3－ニトロフェニル)アミン

3－ジメチルアミノ－1－(2, 4－ジメチルチアゾール－5－イル)プロペノン(20.0g、0.095mol)及び3－ニトロフェニルグアニジン(18.8g)の2－メトキシエタノール(400ml)溶液を20時間加熱還流した。反応液を減圧下濃縮し、残渣に酢酸エチルを加え析出した結晶をろ取することにより(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)－(3－ニトロフェニル)アミン(22.5g、72%)を得た。

1H-NMR: 10.20(1H, s), 8.92(1H, m), 8.61(1H, d, J=5Hz), 8.08(1H, m), 7.82(1H, m), 7.59(1H, dd, J=8Hz, 8Hz), 7.20(1H, d, J=5Hz), 2.67(3H, s), 2.66(3H, s)。

[0093] 製造例4 N－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン

鉄粉(8.5g)の酢酸(50ml)懸濁液を60℃で30分間撹拌した後、水(150ml)及び(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)－(3－ニトロフェニル)アミン(10.0g、30.5mmol)の1, 4－ジオキサン(500ml)溶液を加え60℃で1時間撹拌した。放冷後反応液をろ過し、ろ液を酢酸エチルで抽出し有機層を飽和炭酸水素ナトリウム水溶液で洗浄、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣にジイソプロピルエーテルを加え析出した結晶をろ取することによりN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(8.2g、90%)を得た。

1H-NMR: 9.31(1H, s), 8.47(1H, d, J=5Hz), 7.01(2H, m), 6.92(2H, m), 6.22(1H, m), 4.92(2H, s), 2.65(3H, s), 2.63(3H, s)。

[0094] 実施例1 表1の化合物1

製造例3により得られた(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)－(3－ニトロフェニル)アミン(5.00g、15.3mmol)のN, N－ジメチルホルムア

ミド（100ml）溶液に10％パラジウム炭素（0.50g）を加え、水素ガス雰囲気下室温で6時間30分撹拌した。反応液をろ過し、ろ液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣に酢酸エチルとn－ヘキサンを加え析出した結晶をろ取することによりN－（3－（4－（2，4－ジメチルチアゾール－5－イル）ピリミジン－2－イルアミノ）フェニル）ヒドロキシルアミン（2.05g、43%）を得た。

1H-NMR: 9.48(1H, s), 8.49(1H, d, J=5Hz), 8.22(1H, d, J=2Hz), 8.18(1H, s), 7.38(1H, s), 7.18(1H, d, J=8Hz), 7.05(2H, m), 6.46(1H, d, J=8Hz), 2.65(3H, s), 2.63(3H, s)。

[0095] 実施例2 表1の化合物2

実施例1により得られたN－（3－（4－（2，4－ジメチルチアゾール－5－イル）ピリミジン－2－イルアミノ）フェニル）ヒドロキシルアミン（0.10g、0.32mmol）及びトリエチルアミン（53ul）のテトラヒドロフラン（5ml）溶液に塩化アセチル（25ul）を加え3時間撹拌した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣をシリカゲルクロマトグラフィー（酢酸エチルで溶出）により精製し、酢酸エチルより結晶化することによりN－（3－（4－（2，4－ジメチルチアゾール－5－イル）ピリミジン－2－イルアミノ）フェニル）－N－ヒドロキシアセトアミド（0.04g、35%）を得た。

1H-NMR: 10.52(1H, s), 9.71(1H, s), 8.52(1H, d, J=5Hz), 8.01(1H, s), 7.61(1H, m), 7.26(2H, m), 7.09(1H, d, J=5Hz), 2.65(3H, s), 2.64(3H, s), 2.20(3H, s)。

[0096] 実施例3 表1の化合物3

実施例1により得られたN－（3－（4－（2，4－ジメチルチアゾール－5－イル）ピリミジン－2－イルアミノ）フェニル）ヒドロキシルアミン（0.10g、0.32mmol）及びトリエチルアミン（98ul）のテトラヒドロフラン（5ml）溶液に塩化アセチル（48ul）を加え3時間撹拌した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣をシリカゲルクロマトグラフィー（酢酸エチルで溶出）により精製し、エーテルより結晶化することによりN－アセチル－N－（3－（4－（2，4－ジメチルチアゾール－5－イル）ピリミジン－2－イルアミノ）フェニル）アセトアミド（0.05g、42%）を得た。

1H-NMR: 9.85(1H, s), 8.55(1H, d, J=5Hz), 7.97(1H, brs), 7.76(1H, d, J=8Hz), 7.38(1H, dd, J=8Hz, 8Hz), 7.13(1H, d, J=5Hz), 7.09(1H, d, J=8Hz), 2.65(3H, s), 2.64(3H, s), 2.23(3H, s), 2.06(3H, s)。

[0097] 実施例4 表1の化合物4

n－ブチリルクロリドを用い、表1の化合物2の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－N－ヒドロキシブタンアミドを得た。

1H-NMR: 10.40(1H, s), 9.71(1H, s), 8.52(1H, d, J=5Hz), 8.04(1H, s), 7.59(1H, d, J=7Hz), 7.28(2H, m), 7.09(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 1.61(2H, m), 0.94(3H, J=8Hz)。

[0098] 実施例5 表1の化合物5

n－ブチリルクロリドを用い、表1の化合物3の製造法と同様の操作によりN－ブチリルオキシ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを得た。

1H-NMR: 9.87(1H, s), 8.55(1H, d, J=5Hz), 8.01(1H, s), 7.74(1H, d, J=7Hz), 7.39(1H, m), 7.14(1H, d, J=5Hz), 7.07(1H, d, J=8Hz), 2.64(6H, s), 2.28(2H, m), 1.58(4H, m), 0.90(6H, m)。

[0099] 実施例6 表1の化合物6

ベンゾイルクロリドを用い、表1の化合物2の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－N－ヒドロキシベンズアミドを得た。

1H-NMR: 10.63(1H, s), 9.77(1H, s), 8.52(1H, d, J=5Hz), 8.12(1H, s), 7.65(2H, m), 7.59(1H, m), 7.43(3H, m), 7.29(1H, dd, J=8Hz, 8Hz), 7.13(1H, d, J=9Hz), 7.10(1H, d, J=5Hz), 2.63(3H, s), 2.58(3H, s)。

[0100] 実施例7 表1の化合物7

ベンゾイルクロリドを用い、表1の化合物3の製造法と同様の操作によりN－ベンゾイルオキシ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ベンズアミドを得た。

1H-NMR: 9.86(1H, s), 8.50(1H, d, J=5Hz), 8.15(1H, s), 8.02(2H, d, J=7Hz), 7.76(1H, t, J=8Hz), 7.66(1H, m), 7.60(4H, m), 7.45(1H, m), 7.38(2H, m), 7.31(1H, dd, J=8Hz, 8Hz), 7.12(1H, d, J=5Hz), 7.01(1H, d, J=8Hz), 2.63(3H, s), 2.61(3H, s)。

[0101] 実施例8 表1の化合物8

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(0.30g、1.01mmol)及びトリエチルアミン(0.17ml)のテトラヒドロフラン(10ml)溶液に塩化アセチル(0.08ml)を加え室温で一晩放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣に酢酸エチルを加え析出した結晶をろ取することによりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド(0.23g、67%)を得た。

1H-NMR: 9.83(s, 1H), 9.61(s, 1H), 8.50(d, 1H, J=5Hz), 7.84(s, 1H), 7.52(m, 1H), 7.20(m, 2H), 7.06(d, 1H, J=5Hz), 2.65(s, 3H), 2.63(s, 3H), 2.04(3H, s)。

[0102] 実施例9 表1の化合物9

n－ブチリルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを得た。

1H-NMR: 9.77(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.90(1H, s), 7.47(1H, m), 7.21(2H, m), 7.06(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.28(2H, t, J=7Hz), 1.62(2H, m), 0.93(3H, t, J=7Hz)。

[0103] 実施例10 表1の化合物10

iso－ブチリルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)イソブタンアミドを得た。

1H-NMR: 9.72(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.95(1H, s), 7.44(1H, m), 7.20(2H, m), 7.06(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.62(1H, m), 1.10(6H, d, J=6Hz)。

[0104] 実施例11 表1の化合物11

ベンゾイルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ベンズアミドを得た。

1H-NMR: 10.21(1H, s), 9.67(1H, s), 8.52(1H, d, J=5Hz), 8.15(1H, s), 7.96(2H, d, J=7Hz), 7.55(4H, m), 7.29(2H, m), 7.07(1H, d, J=5Hz), 2.64(3H, s), 2.60(3H, s)。

[0105] 実施例12 表1の化合物12

フェニルアセチルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)フェニルアセトアミドを得た。

1H-NMR: 10.07(1H, s), 9.62(1H, s), 8.50(1H, d, J=5Hz), 7.89(1H, s), 7.50(1H, m), 7.34(4H, m), 7.24(3H, m), 7.06(1H, d, J=5Hz), 3.64(2H, s), 2.63(3H, s), 2.63(3H, s)。

[0106] 実施例13 表1の化合物13

3－フェニルプロピオニルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－3－フェニルプロピオンアミドを得た。

1H-NMR: 9.81(1H, s), 9.59(1H, s), 8.50(1H, d, J=5Hz), 7.87(1H, s), 7.50(1H, d, J=7Hz), 7.26(7H, m), 7.06(1H, d, J=5Hz), 2.92(2H, t, J=8Hz), 2.63(6H, s), 2.62(2H, m)。

[0107] 実施例14 表1の化合物14

シクロプロパンカルボニルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)シクロプロパンカルボキサミドを得た。

1H-NMR: 10.08(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.89(1H, s), 7.49(1H, m), 7.21(2H, m), 7.06(1H, d, J=5Hz), 2.65(3H, s), 2.63(3H, s), 1.82(1H, m), 0.79(4H, m)。

[0108] 実施例15 表1の化合物15

シクロヘキサンカルボニルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)シクロヘキサンカルボキサミドを得た。

1H-NMR: 9.70(1H, s), 9.59(1H, s), 8.50(1H, d, J=5Hz), 7.94(1H, s), 7.43(1H, m), 7.20(2H, m), 7.06(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.35(1H, m), 1.78(4H, m), 1.65(1H, m), 1.42(2H, m), 1.23(3H, m)。

[0109] 実施例16 表1の化合物16

バレリルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ペンタンアミドを得た。

1H-NMR: 9.77(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.89(1H, s), 7.47(1H, m), 7.21(2H, m), 7.06(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.31(2H, t, J=8Hz), 1.58(2H, m), 1.33(2H, m), 0.91(3H, t, J=8Hz)。

[0110] 実施例17 表1の化合物17

n－オクタノイルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)オクタンアミドを得た。

1H-NMR: 9.76(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.89(1H, s), 7.48(1H, m), 7.21(2H, m), 7.06(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.30(2H, t, J=8Hz), 1.59(2H, m), 1.29(8H, m), 0.86(3H, t, J=7Hz)。

[0111] 実施例18 表1の化合物18

2－チオフェンカルボニルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－チオフェンカルボキサミドを得た。

1H-MNR: 10.19(1H, s), 9.69(1H, s), 8.52(1H, d, J=5Hz), 8.11(1H, s), 8.04(1H, d, J=4Hz), 7.85(1H, d, J=6Hz), 7.54(1H, m), 7.28(2H, m), 7.23(1H, m), 7.08(1H, d, J=5Hz), 2.64(3H, s), 2.60(3H, s)。

[0112] 実施例19 表1の化合物19

２－チオフェンアセチルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－(2－チエニル)アセトアミドを得た。

1H-NMR: 10.11(1H, s), 9.64(1H, s), 8.50(1H, d, J=5Hz), 7.90(1H, s), 7.51(1H, m), 7.39(1H, m), 7.23(2H, m), 7.07(1H, d, J=5Hz), 6.99(2H, m), 3.88(2H, s), 2.64(3H, s), 2.63(3H, s)。

[0113] 実施例20 表1の化合物20

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(0.30g、1.01mmol)及びトリエチルアミン(0.32ml)のテトラヒドロフラン(10ml)溶液にピコリノイルクロリド塩酸塩(0.20g)を加え室温で3時間撹拌した。反応液に氷水を加え、析出した結晶をろ取することによりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ピリジン－2－カルボキサミド(0.30g、74%)を得た。

1H-NMR: 10.44(1H, s), 9.71(1H, s), 8.76(1H, d, J=4Hz), 8.53(1H, d, J=5Hz), 8.25(1H, s), 8.18(1H, d, J=8Hz), 8.09(1H, m), 7.69(1H, m), 7.52(2H, m), 7.30(1H, dd, J=8Hz, 8Hz), 7.09(1H, d, J=5Hz), 2.65(3H, s), 2.63(3H, s)。

[0114] 実施例21 表1の化合物21

ニコチノイルクロリド塩酸塩を用い、表1の化合物20の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ピリジン－3－カルボキサミドを得た。

1H-NMR: 10.41(1H, s), 9.71(1H, s), 9.12(1H, d, J=2Hz), 8.77(1H, m), 8.52(1H, d, J=5Hz), 8.29(1H, m), 8.15(1H, m), 7.57(2H, m), 7.31(2H, m), 7.08(1H, d, J=5Hz), 2.64(3H, s), 2.61(3H, s)。

[0115] 実施例22 表1の化合物23

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(0.10g、0.34mmol)、5－メチル－2－チオフェンカルボン酸(53mg)、ジイソプロピルエチルアミン(70ul)のN, N－ジメチルフォルムアミド(5ml)溶液にBOP試薬(ベンゾトリアゾール－1－イルオキシトリス(ジメチルアミ

ノ)ホスホニウムヘキサフルオロホスファイト)(0.18g)を加え室温で一晩放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣をシリカゲルクロマトグラフィー(酢酸エチル:n－ヘキサン＝2:1で溶出)により精製し、酢酸エチルとn－ヘキサンを加え析出した結晶をろ取することによりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－(5－メチルチオフェン)－2－カルボキサミド(0.09g、65%)を得た。

1H-NMR: 10.06(1H, s), 9.67(1H, s), 8.52(1H, d, J=5Hz), 8.08(1H, s), 7.84(1H, m), 7.53(1H, m), 7.26(2H, m), 7.08(1H, d, J=5Hz), 6.92(1H, m), 2.64(3H, s), 2.61(3H, s)。

[0116] 実施例23 表1の化合物25

2, 4－ジメチルチアゾール－5－カルボン酸を用い、表1の化合物23の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－(2、4－ジメチルチアゾール)－5－カルボキサミドを得た。

1H-NMR: 10.02(1H, s), 9.68(1H, s), 8.51(1H, d, J=5Hz), 8.06(1H, s), 7.52(1H, m), 7.23(2H, m), 7.08(1H, d, J=5Hz), 2.66(3H, s), 2.63(3H, s), 2.62(3H, s), 2.55(3H, s)。

[0117] 実施例24 表1の化合物27

塩化クロロアセチルを用い、表1の化合物8の製造法と同様の操作により2－クロロ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 10.21(1H, s), 9.69(1H, s), 8.51(1H, d, J=5Hz), 7.92(1H, s), 7.54(1H, m), 7.24(2H, m), 7.08(1H, d, J=5Hz), 4.25(2H, s), 2.65(3H, s), 2.64(3H, s)。

[0118] 実施例25 表1の化合物28

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(0.30g、1.01mmol)及びトリエチルアミン(0.17ml)のテトラヒドロフラン(10ml)溶液にメタンスルホニルクロリド(86ul)を加え室温で3時間放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾

燥後、減圧下溶媒を留去した。残渣にジイソプロピルエーテルを加え析出した結晶をろ取することによりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)メタンスルホンアミド(0.29g、76%)を得た。

1H-NMR: 9.68(1H, s), 9.65(1H, s), 8.51(1H, d, J=5Hz), 7.61(1H, m), 7.57(1H, m), 7.25(1H, dd, J=8Hz, 8Hz), 7.08(1H, d, J=5Hz), 6.83(1H, m), 3.00(3H, s), 2.65(3H, s), 2.64(3H, s)。

[0119] 実施例26 表1の化合物29

n－ブタンスルホニルクロリドを用い、表1の化合物28の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンスルホンアミドを得た。

1H-NMR: 9.67(2H, s), 8.50(1H, d, J=5Hz), 7.57(2H, m), 7.23(1H, dd, J=8Hz, 8Hz), 7.08(1H, d, J=5Hz), 6.82(1H, d, J=7Hz), 3.09(2H, t, J=8Hz), 1.67(2H, m), 1.35(2H, m), 0.83(3H, t, J=8Hz)。

[0120] 実施例27 表1の化合物30

ベンゼンスルホニルクロリドを用い、表1の化合物28の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ベンゼンスルホンアミドを得た。

1H-NMR: 10.18(1H, s), 9.62(1H, s), 8.49(1H, d, J=5Hz), 7.80(2H, d, J=7Hz), 7.53(5H, m), 7.12(1H, dd, J=8Hz, 8Hz), 7.06(1H, d, J=5Hz), 6.68(1H, d, J=8Hz), 2.65(3H, s), 2.62(3H, s)。

[0121] 実施例28 表1の化合物31

実施例26により得られたN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－クロロアセトアミド(0.10g、0.27mmol)及びモルホリン(47ul)のN, N－ジメチルホルムアミド溶液(5ml)に炭酸カリウム(70mg)及び触媒量のヨウ化カリウムを加え、80℃で2時間撹拌した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣をシリカゲルクロマトグラフィー(クロロホルム:メタノール＝19:1で溶出)により精製し、N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2

－モルホリン－４－イルアセトアミド(0.11g、96%)を得た。

1H-NMR: 9.61(1H, s), 9.60(1H, s), 8.50(1H, d, J=5Hz), 7.92(1H, s), 7.49(1H, d, J=8Hz), 7.24(2H, m), 7.07(1H, d, J=5Hz), 3.64(4H, m), 3.13(2H, s), 2.64(3H, s), 2.64(3H, s), 2.53(4H, m)。

[0122] 実施例29 表1の化合物32

エタノールアミンを用い、表1の化合物31の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－(2－ヒドロキシエチルアミノ)アセトアミドを得た。その後、4N塩酸／酢酸エチルで処理することにより塩酸塩とした。

1H-NMR: 10.48(1H, s), 9.72(1H, s), 8.94(2H, brs), 8.51(1H, d, J=5Hz), 7.91(1H, s), 7.58(1H, m), 7.26(2H, m), 7.09(1H, d, J=5Hz), 3.71(2H, t, J=5Hz), 3.10(2H, m), 2.66(3H, s), 2.64(3H, s)。

[0123] 実施例30 表1の化合物33

１－ｔ－ブトキシカルボニルピペラジンを用い、表1の化合物31の製造法と同様の操作により2－(4－t－ブトキシカルボニルピペラジン－1－イル)－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 9.60(2H, s), 8.50(1H, d, J=5Hz), 7.92(1H, s), 7.49(1H, d, J=8Hz), 7.24(2H, m), 7.07(1H, d, J=5Hz), 3.37(4H, m), 3.16(2H, s), 2.63(6H, s), 1.40(9H, s)。

[0124] 実施例31 表1の化合物35

メトキシアセチルクロリドを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－メトキシアセトアミドを得た。

1H-NMR: 9.62(1H, s), 9.59(1H, s), 8.50(1H, d, J=5Hz), 7.97(1H, s), 7.51(1H, d, J=8Hz), 7.24(2H, m), 7.07(1H, d, J=5Hz), 4.00(2H, s), 3.39(3H, s), 2.64(3H, s), 2.63(3H, s)

実施例32 表1の化合物36

フェニルメタンスルホニルクロリドを用い、表1の化合物28の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)フェニルメタンスルホンアミドを得た。

1H-NMR: 9.79(1H, s), 9.70(1H, s), 8.52(1H, d, J=5Hz), 7.61(2H, m), 7.35(3H, m), 7.31(2H, m), 7.25(1H, dd, J=8Hz, 8Hz), 7.09(1H, d, J=5Hz), 6.81(1H, m), 4.47(2H, s), 2.64(3H, s), 2.62(3H, s)。

[0125] 実施例33 表1の化合物37

4－ブロモブチリルクロリドを用い、表1の化合物8の製造法と同様の操作により4－ブロモ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを得た。

1H-NMR: 9.89(1H, s), 9.62(1H, s), 8.50(1H, d, J=5Hz), 7.90(1H, s), 7.49(1H, m), 7.22(2H, m), 7.06(1H, d, J=5Hz), 3.60(2H, t, J=6Hz), 2.65(3H, s), 2.63(3H, s), 2.12(2H, m)。

[0126] 実施例34 表1の化合物38

N－t－ブトキシカルボニルグリシンを用い、表1の化合物23の製造法と同様の操作により2－(t－ブトキシカルボニルアミノ)－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 9.80(1H, s), 9.64(1H, s), 8.50(1H, d, J=5Hz), 7.87(1H, s), 7.52(1H, m), 7.23(2H, m), 7.06(1H, d, J=5Hz), 6.99(1H, t, J=5Hz), 3.73(2H, d, J=5Hz), 2.65(3H, s), 2.63(3H, s), 1.40(9H, s)。

[0127] 実施例35 表1の化合物39

N－t－ブトキシカルボニル－β－アラニンを用い、表1の化合物23の製造法と同様の操作により3－(t－ブトキシカルボニルアミノ)－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンアミドを得た。

1H-NMR: 9.85(1H, s), 9.62(1H, s), 8.50(1H, d, J=5Hz), 7.88(1H, s), 7.50(1H, d, J=7Hz), 7.21(2H, m), 7.06(1H, d, J=5Hz), 6.82(1H, m), 3.22(2H, dd, J=6, 13Hz), 2.65(3H, s), 2.63(3H, s), 1.38(9H, s)。

[0128] 実施例36 表1の化合物40

Ｎ－ｔ－ブトキシカルボニル－γ－アミノブタン酸を用い、表1の化合物23の製造法と同様の操作により4－(t－ブトキシカルボニルアミノ)－Ｎ－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを得た。

1H-NMR: 9.80(1H, s), 9.61(1H, s), 8.50(1H, d, J=5Hz), 7.89(1H, s), 7.48(1H, d, J=7Hz), 7.21(2H, m), 7.06(1H, d, J=5Hz), 6.83(1H, m), 2.97(2H, dd, J=6, 13Hz), 2.64(3H, s), 2.63(3H, s), 2.30(2H, t, J=7Hz), 1.70(2H, m), 1.38(9H, s)。

[0129] 実施例37 表1の化合物41

実施例34により得られた2－(t－ブトキシカルボニルアミノ)－Ｎ－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド(0.31g、0.68mmol)の1, 4－ジオキサン(10ml)溶液に4N塩酸／1, 4－ジオキサン(5ml)を加え、室温で一晩放置する。反応液を減圧下濃縮し、残渣に酢酸エチルを加え、生じた沈殿をろ取することにより2－アミノ－Ｎ－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド・塩酸塩(0.25g、94%)を得た。

1H-NMR: 10.50(1H, s), 9.78(1H, s), 8.52(1H, d, J=5Hz), 8.21(3H, brs), 7.90(1H, s), 7.58(1H, m), 7.28(2H, m), 7.10(1H, d, J=5Hz), 3.78(2H, m), 2.67(3H, s), 2.65(3H, s)。

[0130] 実施例38 表1の化合物42

実施例35により得られた3－(t－ブトキシカルボニルアミノ)－Ｎ－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンアミドを用い、表1の化合物41の製造法と同様の操作により3－アミノ－Ｎ－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンアミドを得た。

1H-NMR: 10.11(1H, s), 9.68(1H, s), 8.51(1H, d, J=5Hz), 7.88(4H, m), 7.52(1H, d, J=8Hz), 7.26(2H, m), 7.08(1H, d, J=5Hz), 3.08(2H, m), 2.73(2H, t, J=7Hz), 2.66(3H, s), 2.64(3H, s)。

[0131] 実施例39 表1の化合物43

実施例36により得られた4－(t－ブトキシカルボニルアミノ)－Ｎ－(3－(4－(2, 4

－ジメチルチアゾール－５－イル）ピリミジン－２－イルアミノ）フェニル）ブタンアミドを用い、表１の化合物４１の製造法と同様の操作により４－アミノ－Ｎ－（３－（４－（２，４－ジメチルチアゾール－５－イル）ピリミジン－２－イルアミノ）フェニル）ブタンアミドを得た。

1H-NMR: 9.96(1H, s), 9.65(1H, s), 8.51(1H, d, J=5Hz), 7.89(4H, m), 7.51(1H, d, J=8Hz), 7.23(2H, m), 7.07(1H, d, J=5Hz), 2.85(2H, m), 2.66(3H, s), 2.64(3H, s), 2.44(2H, t, J=7Hz), 1.87(2H, m)。

[0132] 実施例４０ 表１の化合物４７

２，２，２－トリフルオロエタンスルホニルクロリドを用いて、表１の化合物２８の製造法と同様の操作によりＮ－（３－（４－（２，４－ジメチルチアゾール－５－イル）ピリミジン－２－イルアミノ）フェニル）－（２，２，２－トリフルオロエタン）スルホンアミドを得た。

1H-NMR: 10.37(1H, s), 9.69(1H, s), 8.51(1H, d, J=5Hz), 7.67(1H, m), 7.58(1H, m), 7.27(1H, dd, J=8Hz, 8Hz), 7.09(1H, d, J=5Hz), 6.84(1H, dd, J=6, 8Hz), 4.46(2H, J=9Hz), 2.65(3H, s), 2.64(3H, s)。

[0133] 実施例４１ 表１の化合物４８

製造例４により得られたＮ－（４－（２，４－ジメチルチアゾール－５－イル）ピリミジン－２－イル）ベンゼン－１，３－ジアミン（0.10g、0.34mmol）のジクロロメタン（5ml）溶液にイソシアン酸フェニル（40ul）を加え室温で一晩放置した。反応液を減圧下濃縮し、残渣に酢酸エチルを加え、析出した結晶をろ取することによりＮ－（３－（４－（２，４－ジメチルチアゾール－５－イル）ピリミジン－２－イルアミノ）フェニル）－Ｎ’－フェニルウレア（0.1.g、71%）を得た。

1H-NMR: 9.62(1H, s), 8.64(1H, s), 8.55(1H, s), 8.51(1H, d, J=5Hz), 7.74(1H, s), 7.45(3H, m), 7.28(2H, m), 7.20(2H, m), 7.07(1H, d, J=5Hz), 6.96(1H, t, J=7Hz), 2.64(3H, s), 2.62(3H, s)。

[0134] 実施例４２ 表１の化合物４９

イソシアン酸酢酸エチルを用い、表１の化合物４８の製造法と同様の操作によりＮ－（３－（４－（２，４－ジメチルチアゾール－５－イル）ピリミジン－２－イルアミノ）フェニル）－Ｎ’－エトキシカルボニルメチルウレアを得た。

1H-NMR: 9.56(1H, s), 8.67(1H, s), 8.50(1H, d, J=5Hz), 7.62(1H, s), 7.41(1H, m), 7.15(2H, m), 7.05(1H, d, J=5Hz), 6.46(1H, t, J=6Hz), 4.12(2H, q, J=7Hz), 3.87(2H, d. J=6Hz), 2.65(3H, s), 2.63(3H, s), 1.21(t, J=7Hz)。

[0135] 実施例43 表1の化合物50

実施例42により得られたN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル) －N'－エトキシカルボニルメチルウレア(0.20g、0.47mmol)のテトラヒドロフラン(6ml)及びメタノール(4ml)溶液に4M水酸化リチウム水溶液(0.59ml)を加え、60℃で30分間撹拌した。反応液を室温まで冷却した後、水と1N塩酸水溶液を加え液性を酸性にして室温で放置した。生じた沈殿をろ取することにより(3－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ウレイド)酢酸(0.17g、91%)を得た。

1H-NMR: 12.52(1H, brs), 9.55(1H, s), 8.64(1H, s), 8.50(1H, d, J=5Hz), 7.61(1H, s), 7.39(1H, m), 7.16(2H, m), 7.05(1H, d, J=5Hz), 6.37(1H, t, J=6Hz), 3.80(2H, d, J=6H,), 2.65(3H, s), 2.64(3H, s)。

[0136] 実施例44 表1の化合物51

3, 3, 3－トリフルオロプロピオン酸を用い、表1の化合物23の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル) －(3, 3, 3－トリフルオロプロパン)アミドを得た。

1H-NMR: 10.20(1H, s), 9.69(1H, s), 8.52(1H, d, J=5Hz), 7.92(1H, s), 7.54(1H, d, J=8Hz), 7.25(2H, m), 7.08(1H, d, J=5Hz), 3.51(2H, q, J=9Hz), 2.64(3H, s), 2.64(3H, s)。

[0137] 実施例45 表1の化合物52

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミン(0.10g、0.34mmol)、4－(ジメチルアミノ)ブタン酸・塩酸塩(62mg)、ジイソプロピルエチルアミン(140ul)のN, N－ジメチルフォルムアミド(5ml)溶液にBOP試薬(ベンゾトリアゾール－1－イルオキシトリス(ジメチルアミノ)ホスホニウムヘキサフルオロホスファイト) (0.18g)を加え室温で一晩放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を

留去した。残渣を酢酸エチルに溶解した後、4N塩酸／酢酸エチル溶液を加え減圧下溶媒を留去した。残渣に酢酸エチルを加え生じる沈殿をろ取することにより4－ジメチルアミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミド・塩酸塩(0.06g、39%)を得た。

1H-NMR: 10.35(1H, brs), 10.02(1H, s), 9.69(1H, s), 8.51(1H, d, J=5Hz), 7.88(1H, s), 7.51(1H, d, J=9Hz), 7.24(2H, m), 7.08(1H, d, J=5Hz), 3.07(2H, m), 2.76(3H, s), 2.75(3H, s), 2.66(3H, s), 2.64(3H, s), 2.44(2H, t, J=7Hz), 1.97(2H, m)。

[0138] 実施例46 表1の化合物53

イソチオシアン酸メチルを用い、表1の化合物48の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－N'－メチルチオウレアを得た。

1H-NMR: 9.72(1H, s), 9.48(1H, brs), 8.53(1H, d, J=5Hz), 7.83(1H, s), 7.60(1H, brs), 7.55(1H, d, J=8Hz), 7.25(1H, dd, J=8Hz, 8Hz), 7.10(1H, d, J=5Hz), 6.92(1H, d, J=8Hz), 2.90(3H, d, J=4Hz), 2.66(3H, s), 2.64(3H, s)。

[0139] 実施例47 表1の化合物55

3－(3－ピリジル)プロピオン酸を用い、表1の化合物23の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－3－(ピリジン－3－イル)プロパンアミドを得た。

1H-NMR: 9.84(1H, s), 9.62(1H, s), 8.50(1H, d, J=5Hz), 8.40(1H, d, J=5Hz), 7.86(1H, s), 7.67(1H, d, J-8Hz), 7.50(1H, m), 7.31(1H, m), 7.21(2H, m), 7.06(1H, d, J=5Hz), 2.94(2H, t, J=8Hz), 2.66(2H, t, J=8Hz), 2.64(3H, s), 2.63(3H, s)。

[0140] 実施例48 表1の化合物56

3－クロロプロパンスルホニルクロリドを用いて、表1の化合物28の製造法と同様の操作により3－クロロ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンスルホンアミドを得た。

1H-NMR: 9.81(1H, s), 9.69(1H, s), 8.51(1H, d, J=5Hz), 7.59(2H, m), 7.25(1H, dd, J=8Hz, 8Hz), 7.09(1H, d, J=5Hz), 6.83(1H, d, J=8Hz), 3.73(2H, t, J=6Hz), 3.24(2H, m), 2.65(3H, s), 2.64(3H, s), 2.14(2H, m)。

[0141] 実施例49 表1の化合物58

4－(ブロモメチル)ベンゼンスルホニルクロリドを用いて、表1の化合物28の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－4－ブロモメチルベンゼンスルホンアミドを得た。

1H-NMR: 10.24(1H, s), 9.66(1H, s), 8.50(1H, d, J=5Hz), 7.80(2H, m), 7.55(4H, m), 7.13(1H, dd, J=8Hz, 8Hz), 7.07(1H, d, J=5Hz), 6.68(1H, d, J=8Hz), 4.74(2H, d, J=34Hz), 2.65(3H, s), 2.62(3H, s)。

[0142] 実施例50 表1の化合物59

クロロ炭酸ベンジルを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ベンジルオキシカルボキサミドを得た。

1H-NMR: 9.68(1H, s), 9.60(1H, s), 8.49(1H, d, J=5Hz), 7.82(1H, s), 7.42(6H, m), 7.19(1H, dd, J=8Hz, 8Hz), 7.06(1H, d, J=5Hz), 5.15(2H, s), 2.63(6H, s)。

[0143] 実施例51 表1の化合物60

クロロ炭酸エチルを用い、表1の化合物8の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)エトキシカルボキサミドを得た。

1H-NMR: 9.59(1H, s), 9.50(1H, s), 8.49(1H, d, J=5Hz), 7.81(1H, s), 7.46(1H, d, J=8Hz), 7.18(1H, dd, J=8Hz, 8Hz), 7.05(2H, m), 4.12(2H, q, J=7Hz), 2.64(3H, s), 2.63(3H, s), 1.25(3H, t, J=7Hz)。

[0144] 実施例52 表1の化合物62

3－アセトアミドフェニルグアニジンと製造例2により得られた3－ジメチルアミノ－1－(4, 5－ジメチルチアゾール－2－イル)プロペノンを用い、参考例3と同様の操作によりN－(3－(4－(4, 5－ジメチルチアゾール－2－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 9.83(1H, s), 9.73(1H, s), 8.53(1H, m), 7.82(1H, s), 7.55(1H, m), 7.33(1H, m), 7.21(2H, m), 2.42(3H, s), 2.34(3H, s), 2.02(3H, s)。

[0145] 実施例53 表1の化合物67

製造例4により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 4－ジアミンを用い、表1の化合物8の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド得た。

1H-NMR: 9.80(1H, s), 9.54(1H, s), 8.48(1H, d, J=5Hz), 7.66(2H, d, J=9Hz), 7.49(2H, d, J=9Hz), 7.04(1H, d, J=5Hz), 2.65(3H, s), 2.63(3H, s), 2.02(3H, s)。

[0146] 実施例54 表1の化合物82

3－アセトアミドフェニルグアニジンとShudong Wangら(Jounal of Medicinal Chemistry、47巻1662～1675項2004年)の方法により得られるN'－(5―(3―ジメチルアミノアクリロイル)－4－メチルチアゾール－2－イル)―N, N－ジメチルホルムアミジンを用い、製造例3と同様の操作によりN－(3－(4－(2－アミノ－4－メチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 9.82(1H, s), 9.37(1H, s), 8.29(1H, d, J=5Hz), 7.72(1H, s), 7.54(1H, d, J=8Hz), 7.47(2H, s), 7.16(2H, m), 6.83(1H, d, J=5Hz), 2.42(3H, s), 2.01(3H, s)。

[0147] 実施例55 表1の化合物83

3－アセトアミドフェニルグアニジンと製造例2と同様の方法で得られた3－ジメチルアミノ－1－(4－メチル－2－メチルアミノチアゾール－5－イル)プロペノンを用い、製造例3と同様の操作によりN－(3－(4－(4－メチル－2－メチルアミノチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。

1H-NMR: 9.81(1H, s), 9.37(1H, s), 8.29(1H, d, J=5Hz), 8.01(1H, d, J=5Hz), 7.78(1H, s), 7.47(1H, J=8Hz), 7.16(2H, m), 6.85(1H, d, J=6Hz), 2.83(3H, d, J=5Hz), 2.45(3H, s), 2.01(3H, s)。

[0148] 実施例56 表1の化合物103

実施例1により得られたN－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 4－ジアミンを用い、表1の化合物28の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)メタンスルホンアミドを得た。

1H-NMR: 9.64(1H, s), 9.42(1H, s), 8.50(1H, d, J=5Hz), 7.73(2H, d, J=9Hz),

7.16(2H, d, J=9Hz), 7.07(1H, d, J=5Hz), 2.93(3H, s), 2.66(3H, s), 2.63(3H, s)。

[0149] 実施例57 表1の化合物104

2, 2, 2－トリフルオロエタンスルホニルクロリドを用いて、表1の化合物103の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－(2, 2, 2－トリフルオロエタン)スルホンアミドを得た。

1H-NMR: 10.15(1H, s), 9.68(1H, s), 8.51(1H, d, J=5Hz), 7.75(2H, d, J=8Hz), 7.17(2H, d, J=8Hz), 7.09(1H, d, J=5Hz), 4.41(2H, q, J=9Hz), 2.66(3H, s), 2.63(3H, s)。

[0150] 実施例58 表1の化合物105

フェニルメタンスルホニルクロリドを用い、表1の化合物103の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)フェニルメタンスルホンアミドを得た。

1H-NMR: 9.63(1H, s), 9.59(1H, s), 8.51(1H, d, J=5Hz), 7.72(2H, d, J=9Hz), 7.33(5H, m), 7.15(2H, d, J=9Hz), 7.07(1H, d, J=5Hz), 4.39(2H, s), 2.66(3H, s), 2.63(3H, s)。

[0151] 実施例59 表1の化合物106

2－チオフェンカルボニルクロリドを用い、表1の化合物67の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－チオフェンカルボキサミドを得た。

1H-MNR: 10.14(1H, s), 9.64(1H, s), 8.51(1H, d, J=5Hz), 8.00(1H, d, J=3Hz), 7.83(1H, d, J=6Hz), 7.74(2H, d, J=8Hz), 7.64(2H, d, J=8Hz), 7.22(1H, dd, J=3Hz, 6Hz), 7.07(1H, d, J=5Hz), 2.66(3H, s), 2.64(3H, s)。

[0152] 実施例60 表1の化合物54

イソチオシアン酸フェニルを用い、表1の化合物48の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－N'－フェニルチオウレアを得た。

1H-NMR: 9.74(1H, s), 9.70(1H, s),9.67(1H, s), 8.51(1H, d, J=5Hz), 7.91(1H, s), 7.57(1H, d, J=8Hz), 7.50(1H, d, J=8Hz), 7.29(3H, m), 7.09(3H, m), 2.64(3H, s),

2.62(3H, s)。

[0153] 実施例61 表1の化合物26

3－クロロチオフェン－2－カルボン酸を用い、表1の化合物23の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－(3－クロロチオフェン)カルボキサミドを得た。

1H-NMR: 10.10(1H, s), 9.70(1H, s), 8.52(1H, d, J=5Hz), 8.10(1H, s), 7.91(1H, d, J=5Hz), 7.52(1H, m), 7.28(2H, m), 7.21(1H, d, J=5Hz), 7.09(1H, d, J=5Hz), 2.64(3H, s), 2.62(3H, s)。

[0154] 実施例62 表1の化合物44

実施例37により得られた2－アミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド・塩酸塩(0.10g、0.26mmol)及びトリエチルアミン(0.06ml)のテトラヒドロフラン(5ml)溶液に塩化アセチル(0.02ml)を加え室温で一晩放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣に酢酸エチルを加え析出した結晶をろ取することにより2－アセチルアミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミド(0.06g、58%)を得た。

1H-NMR: 9.86(1H, s), 9.64(1H, s), 8.50(1H, d, J=5Hz), 8.16(1H, m), 7.88(1H, s), 7.52(1H, m), 7.23(2H, m), 7.07(1H, d, J=5Hz), 3.87(2H, d, J=6Hz), 2.65(3H, s), 2.63(3H, s), 1.89(3H, s)。

[0155] 実施例63 表1の化合物45

実施例38により得られた3－アミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンアミドを用い、表1の化合物44の製造法と同様の操作により3－アセチルアミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンアミドを得た。

1H-NMR: 9.86(1H, s), 9.64(1H, s), 8.50(1H, d, J=5Hz), 8.16(1H, m), 7.88(1H, s), 7.52(1H, m), 7.23(2H, m), 7.07(1H, d, J=5Hz), 3.87(2H, d, J=6Hz), 2.65(3H, s), 2.63(3H, s), 1.89(3H, s)。

[0156] 実施例64 表1の化合物46

実施例39により得られた4－アミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを用い、表1の化合物44の製造法と同様の操作により4－アセチルアミノ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ブタンアミドを得た。

1H-NMR: 9.86(1H, s), 9.62(1H, s), 8.50(1H, d, J=5Hz), 7.92(1H, m), 7.87(1H, s), 7.50(1H, d, J=8Hz), 7.23(2H, m), 7.06(1H, d, J=5Hz), 2.65(3H, s), 2.63(3H, s), 1.79(3H, s)。

[0157] 実施例65 表1の化合物119

塩化クロロアセチルを用い、表1の化合物67の製造法と同様の操作により2－クロロ－N－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを得た。さらに表1の化合物31の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－モルホリン－4－イルアセトアミドを得た。その後、4N塩酸／酢酸エチルで処理することにより塩酸塩とした。

1H-NMR: 9.60(1H, s), 9.58(1H, s), 8.49(1H, d, J=5Hz), 7.69(2H, d, J=9Hz), 7.55(2H, d, J=9Hz), 7.06(1H, d, J=5Hz), 3.65(4H, m), 3.11(2H, s), 2.65(3H, s), 2.63(3H, s)。

[0158] 実施例66 表1の化合物120

実施例65により得られた2－クロロ－N－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)アセトアミドを用い、表1の化合物32の製造法と同様の操作によりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－2－(2－ヒドロキシエチルアミノ)アセトアミドを得た。その後、4N塩酸／酢酸エチルで処理することにより塩酸塩とした。

1H-NMR: 10.56(1H, s), 9.69(1H, s), 8.95(2H, brs), 8.51(1H, d, J=5Hz), 7.72(2H, d, J=9Hz), 7.54(2H, d, J=9Hz), 7.08(1H, d, J=5Hz), 3.96(2H, m), 3.10(2H, m), 2.67(3H, s), 2.64(3H, s)。

[0159] 実施例67 表1の化合物108

ニコチン酸クロリドを用い、表1の化合物67の製造法と同様の操作によりN－(4－(

4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)ニコチンアミドを得た。

1H-NMR: 10.40(1H, s), 9.66(1H, s), 9.11(1H, d, J=2Hz), 8.76(1H, dd, J=2Hz, 5Hz), 8.51(1H, d, J=5Hz), 8.31(1H, dt, J=2Hz, 8Hz), 7.76(2H, d, J=8Hz), 7.70(2H, d, J=8Hz), 7.57(1H, dd, J=5Hz, 8Hz), 7.07(1H, d, J=5Hz), 2.66(3H, s), 2.65(3H, s)。

[0160] 実施例68 表1の化合物135

1－アセチルピペリジン－4－カルボン酸を用い、表1の化合物23の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)1－アセチルピペリジン－4－カルボンキシアミドを得た。

1H-NMR: 9.85(1H, s), 9.62(1H, s), 8.50(1H, d, J=4Hz), 7.47(1H, dt, J=2Hz, 8Hz), 7.22(2H, m), 7.06(1H, d, J=4Hz), 4.41(1H, m), 3.88(1H, m), 3.05(1H, m), 2.66(3H, s), 2.65(3H, s), 2.65-2.55(2H, m), 2.01(3H, s), 1.85-1.70(2H, m), 1.60(1H, m), 1.45(1H, m)。

[0161] 実施例69 表1の化合物57

実施例48により得られた3－クロロ－N－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)プロパンスルホンアミド(0.23g、0.52mmol)にモルホリン(10ml)を加え70℃にて一晩放置した。反応液に水を加え、酢酸エチルで抽出し、硫酸マグネシウムで乾燥後、減圧下溶媒を留去した。残渣に酢酸エチルを加え析出した結晶をろ取することによりN－(4－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)フェニル)－3－モルホリノプロパンスルホンアミド(0.18g、70%)を得た。

1H-NMR: 9.78(1H, s), 9.73(1H, s), 8.51(1H, d, J=5Hz), 7.64-7.56(2H, m), 7.24(1H, d, J=8Hz), 7.09(1H, d, J=5Hz), 6.83(1H, t, J=8Hz), 3.41(4H, s), 3.16(2H, t, J=6Hz), 2.65(3H, s), 2.64(3H, s) 2.30(2H, t, J=6Hz), 2.19(4H, s), 1.82(2H, m)。

[0162] 実施例70 表1の化合物70

4－メチル－3－ニトロフェニルグアニジンを用い製造例3及び4と同様の方法により4－メチル－N－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イル)ベンゼン－1, 3－ジアミンを得た。得られた上記化合物を用い表1の化合物8の製造

法と同様の操作によりN－(5－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)－2－メチルフェニル)アセトアミドを得た。

1H-NMR: 9.57(1H, s), 9.28(1H, s), 8.49(1H, d, J=5Hz), 7.76(1H, s), 7.53(1H, d, J=8Hz), 7.11(1H, d, J=8Hz), 7.05(1H, d, J=5Hz), 2.64(3H, s), 2.63(3H, s), 2.13(3H, s), 2.05(3H, s)。

[0163] 実施例71 表1の化合物69

2－メチル－5－ニトロフェニルグアニジンを用い表1の化合物70の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)－4－メチルフェニル)アセトアミドを得た。

1H-NMR: 9.80(1H, s), 8.86(1H, s), 8.39(1H, d, J=5Hz), 7.63(1H, d, J=2Hz), 7.31(1H, dd, J=2Hz&8Hz), 7.12(1H, d, J=8Hz), 6.95(1H, d, J=5Hz), 2.61(3H, s), 2.54(3H, s), 2.14(3H, s), 2.01(3H, s)。

[0164] 実施例72 表1の化合物68

2－メチル－3－ニトロフェニルグアニジンを用い表1の化合物70の製造法と同様の操作によりN－(3－(4－(2, 4－ジメチルチアゾール－5－イル)ピリミジン－2－イルアミノ)－2－メチルフェニル)アセトアミドを得た。

1H-NMR: 9.32(1H, s), 8.90(1H, s), 8.38(1H, d, J=5Hz), 7.25(1H, d, J=2Hz), 7.18(1H, d, J=8Hz), 7.12(1H, t, J=8Hz), 6.95(1H, d, J=5Hz), 2.61(3H, s), 2.55(3H, s), 2.07(3H, s), 2.05(3H, s)。

[0165] 薬理実験例1 オーロラ2キナーゼ活性阻害作用

(1)オーロラ2キナーゼの調製

Hela細胞(ATCC No.CCL-2)から常法に従いTotal RNAを抽出し、逆転写酵素反応によりcDNAを合成した。当該cDNAを鋳型としてPCR反応を行った。PCR反応に供したプライマー配列は配列番号1(5'-GGA ATT CCA TAT GGA CCG ATC TAA AGA AAA CTG-3')及び配列番号2(5'-GGG GGG CTC GAG AGA CTG TTT GCT AGC TGA TTC-3')である。

[0166] 当該PCR反応により得られた配列は、先に引用した文献(Tne EMBO Journal Vol.17 No.11 p3052-3065 1998)に報告されているオーロラ2キナーゼコード遺伝

子の配列と同一であった。

[0167] 増幅させたオーロラ2キナーゼコード遺伝子を、大腸菌発現ベクターpET32a(Novagen社製)に導入し、組換え体を作製した。組換え体は、Ambrookらの「分子クローニング-実験マニュアル、第二版(1989 Cold Spring Harbor Laboratory press)」、及びAusubelらの「分子生物学における現在のプロトコール、(1999 John Wiley and Sons Inc.)」に従い得ることができる。

[0168] その後、組換え体をタンパク大量発現用大腸菌BL21R株(Novagen社)に導入し、オーロラ2キナーゼ大量発現用大腸菌株を作製した。

[0169] オーロラ2キナーゼ大量発現用大腸菌株をAmpicilin(50 ug/ml)を含有するLB培地で培養した。37℃で1時間振とう培養した後に、オーロラ2キナーゼを発現誘導するために、培養温度を25℃に設定し、終濃度0.1mM IPTG(SIGMA社)を添加し、25℃にて24時間振とう培養した。その後、培養液を7000rpm 10分遠心分離し、菌体を回収した。

[0170] 回収した菌体を36mlのlysis buffer[50mM Tris pH6.8, 150mM NaCl, 20mM β-Glycerophspate, 0.3mM Na3V04, 50mM NaF, 2mM PMSF(フッ化フェニルメチルスルフォニル), プロテアーゼ阻害剤カクテル錠(ベーリンガーマンハイム社) 1錠]に懸濁し、超音波破砕をした。さらに、蛋白質間非特異的結合を解離させるために4mlの10%NP-40(和光純薬)を添加した。

[0171] その後、液中の組換えオーロラ2キナーゼをNi-NTA agaroseビーズ (QIAGEN社)に吸着させ、組換えオーロラ2キナーゼが吸着したビーズを50mlのK buffer (1M KCl/1xTNT)、G buffer (30%Glycerol, 0.5M KCl/ 1xTNT)で洗浄し、オーロラ2キナーゼを取得した。

[0172] (2)オーロラ2キナーゼアッセイ

各ウェルに酵素反応用緩衝液(200mM Tris-HCl(pH7.0)、100mM MgCl2)1.5μl、50mM ジチオスレイトール1.5μl、1mM ペプチド基質[LRRASLG]1.5μl、及び、化合物を添加したDMSO溶液1.5μlを加えた。

[0173] 酵素希釈液[50mM Tris-HCl (pH6.8)、200mM NaCl、50% グリセロール、1mg/ml BSA]中にて希釈したオーロラ2キナーゼ(1mg/ml) 1.5μlを「ブランク」ウエル以外の

全てのウエルに添加した。オーロラ2キナーゼを含まない酵素希釈液1.5μlを「ブランク」ウエルに添加した。「トータル」ウエルには、化合物未添加のDMSO溶液を1.5μl加えた。

[0174] 次に、全ての試験ウエルに、1.2μCi[(32P)ATP(室町薬品、比活性>3500Ci/mmol)]を含有する30μM ATP溶液5ulを添加して、室温で60分間インキュベートし、反応混合物5μLをホスホセルロース(Wattman、p81)フィルター上にスポッティングし、リン酸化された32P－標識ペプチドをフィルター上に吸着させた。その後フィルターを0.75%リン酸溶液で3回洗浄して未反応物を除去し、反応した32PをBAS5000(FUJIFILM社)を用いて計数した。

[0175] 「ブランク」(酵素なし)の計数値を0%とし、「トータル」(化合物なし)の計数値を100%とし、これら対照値を使用して、酵素活性のIC50値を決定した。

[0176] (3)評価結果

前述の(2)オーロラ2キナーゼアッセイの操作手順に従い化合物を評価した結果、本発明の式(I)の化合物がオーロラ2キナーゼ活性を阻害することが認められた。その結果を表2に示す。表2に示す「化合物」欄は、表1に記載されている化合物番号をそれぞれ示す。

[0177] [表2]

化合物	IC50値(nM)
26	20
44	8
45	8
46	5
54	16
108	15
119	37
120	71
135	4

[0178] この結果より、本発明の実施例で示された化合物は、強力なオーロラ2キナーゼ活性阻害作用を示すことが明らかとなった。

産業上の利用可能性

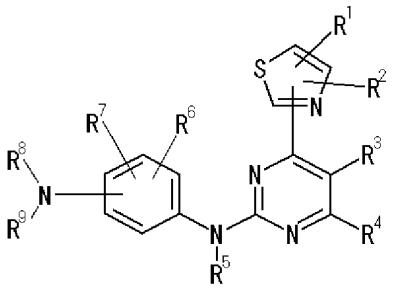
[0179] 本発明によれば、新規なアミノピリミジン化合物を提供することができる。

[0180] なお本出願は、2004年5月20日付で出願された日本特許出願(特願2004－150962号)に基づいており、その全体が引用により援用される。

請求の範囲

[1] 下記式(I)

[化1]



(I)

[式中、R^1及びR^2は、同一又は異なってハロゲン原子、アルキル、ヒドロキシ、アルコシキ、アミノ、アルキルアミノ又はアシルアミノを示し、

R^3及びR^4は同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ又はアルコキシを示し、

R^5は水素原子、アルキル又はアシルを示し、

R^6及びR^7は、同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ、アルコキシ、アミノ、アルキルアミノ、アシルアミノ、カルバモイル、アルキルカルバモイル、カルボキシ、アルコキシカルボニル、スルファモイル、アルキルスルファモイル、ニトロ又はシアノを示し、

R^8はCOR^{10}、CO_2R^{10}、$CONR^{10}R^{11}$、$CSNR^{10}R^{11}$、SO_2R^{10}又はOR^{10}を示し[式中、R^{10}及びR^{11}は、同一又は異なって$-T-R^{12}${式中、Tは、存在しないか、C_{1-6}のアルキレン、C_{2-6}のアルケニレン、C_{2-6}のアルキニレン又はそのアルキレン、アルケニレン、アルキニレンのうち1から3個のメチレンを$-C(=O)-$、$-C(=O)O-$、$-OC(=O)-$、$-C(=O)N(R^{14})-$、$-OC(=O)N(R^{14})-$、$-NR^{14}-$、$-N(R^{14})O-$、$N(R^{14})C(=O)-$、$-N(R^{14})C(=O)O-$、$-N(R^{14})C(=O)N(R^{15})-$、$-S(O_2)-$、$NR^{14}S(O_2)-$、$-S(O_2)N(R^{14})-$、$-N(R^{14})C(NH)N(R^{15})-$、酸素原子又は硫黄原子で置換したもののいずれかを示し(式中、R^{14}及びR^{15}は、同一又は異なって水素又はアルキルを示す。)、R^{12}は水素、ハロゲン原子、ヒドロキシ、アルキル、アミノ、シクロアルキル、複素環又はアリールを示す。}又はR^{10}とR^{11}が相互に結合する窒素原子とともに5から7員環を形成する基を示す。]、

R^9は水素原子、アルキル、ヒドロキシ、アルコキシ又はアシルを示すが、R^8がOR^{10}を示す場合は、R^9は水素原子を示し、又は、

R^8及びR^9は、相互に結合する窒素原子とともに5から7員環を形成する基を示す。]で表される化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[2] 上記式(I)中、R^3及びR^4は、同一又は異なって水素原子又はアルキルを示し、

R^6及びR^7は、同一又は異なって水素原子、ハロゲン原子、アルキル、ヒドロキシ又はアルコキシを示し、

R^8はCOR^{10}、$CONR^{10}R^{11}$、SO_2R^{10}又はOR^{10}示し[式中、R^{10}及びR^{11}は、同一又は異なって－T－R^{12}{式中、Tは、存在しないか、C_{1-6}のアルキレン又はそのアルキレンのうち1から3個のメチレンを－C(＝O)－、－C(＝O)O－、－C(＝O)N(R^{14})－、－N(R^{14})－、－N(R^{14})C(＝O)－又は酸素原子で置換したもののいずれかを示す。}又はR^{10}とR^{11}が相互に結合する窒素原子とともに、さらに、酸素原子、硫黄原子及びNHから選ばれるヘテロ原子を含んでいてもよく、置換基を有していてもよい5から7員環を形成する基を示す。]、

R^9は水素原子、アルキル又はアシルを示すか、又は、

R^8及びR^9は、相互に結合する窒素原子とともに5から7員環を形成する基を示す請求項1に記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[3] 上記式(I)中、R^1及びR^2が同一又は異なって、アルキル又はアシルアミノを示す請求項1又は2に記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[4] 上記式(I)中、R^3及びR^4がそれぞれ水素原子を示す請求項1から3のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[5] 上記式(I)中、R^5が水素原子を示す請求項1から3のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[6] 上記式(I)中、R^3及びR^4がそれぞれ水素原子を示し、R^5が水素原子を示す請求項1から5のいずれかに記載の化合物、医薬上許容しうる塩、水和物、水付加物又は溶媒和物。

[7] 請求項1から6で表されるアミノピリミジン化合物又はその医薬上許容される塩、水和物、水付加物及び溶媒和物を含有することを特徴とする癌の予防及び／又は治療

剤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/009119

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D417/04, A61K31/506, 31/5377, 31/551, A61P35/00, C07D417/14//
A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D417/04, A61K31/506, 31/5377, 31/551, A61P35/00, C07D417/14//
A61P43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus(STN), EMBASE(STN), MEDLINE(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Campbell M, Shudong W, Sian A. et al., Structural Determinants of CDK4 Inhibition and Design of Selective ATP Competitive Inhibitors, Chemistry & Biology, April, 2004, Vol.11, pages 525 to 534., Introduction; table 3; compound Nos. 5 to 10	1-6 1-7
Y	JP 2003-528872 A (CYCLACEL LTD.), 30 September, 2003 (30.09.03), Claims 1 to 4 & WO 2001/072745 A1 & US 2002/0019404 A1 & EP 1274705 A1	1-7

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 July, 2005 (29.07.05)	16 August, 2005 (16.08.05)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2005/009119

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 8-503971 A (CIBE-GEIGY AG.), 30 April, 1996 (30.04.96), Claims 1, 6, 9 to 11; page 31, line 19 to] page 37, line 10 & WO 95/09847 A1 & EP 672035 A1 & US 5612340 A	1,2,4-7
A	WO 2002/096905 A1 (Vertex Pharmaceuticals Inc.), 05 December, 2002 (05.12.02), Claims 1, 7, 11, 13 & US 2003/0119856 A1 & EP 1392684 A1	1-7
P,X	WO 2004/043953 A1 (CYCLACEL LTD.), 27 May, 2004 (27.05.04), Claims; table 1; compound Nos. 1, 45; table 2 & AU 2003/301977 A1	1-7
E,X	WO 2005/052147 A2 (CYCLACEL LTD.), 09 June, 2005 (09.06.05), Claims 16, 45 to 50 (Family: none)	1-7

国際調査報告

国際出願番号 ＰＣＴ／ＪＰ２００５／００９１１９

A. 発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl.[7] C07D417/04, A61K31/506, 31/5377, 31/551, A61P35/00, C07D417/14 // A61P43/00

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl.[7] C07D417/04, A61K31/506, 31/5377, 31/551, A61P35/00, C07D417/14 // A61P43/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAplus(STN), EMBASE(STN), MEDLINE(STN)

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X Y	Campbell M, Shudong W, Sian A, et.al. Structural Determinants of CDK4 Inhibition and Design of Selective ATP Competitive Inhibitors, Chemistry & Biology, April, 2004, Vol.11, Page 525-534. Introduction, 表３の化合物５～１０など	1-6 1-7
Y	JP 2003-528872 A（サイクラセル・リミテッド）2003.09.30 特許請求の範囲１～４など	1-7

☑ Ｃ欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「Ａ」特に関連のある文献ではなく、一般的技術水準を示すもの
「Ｅ」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「Ｌ」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「Ｏ」口頭による開示、使用、展示等に言及する文献
「Ｐ」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「Ｔ」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「Ｘ」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Ｙ」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「＆」同一パテントファミリー文献

国際調査を完了した日 ２９．０７．２００５	国際調査報告の発送日 16.8.2005
国際調査機関の名称及びあて先 日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員） 髙岡　裕美 電話番号　０３－３５８１－１１０１　内線　３４５１

4C 3337

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（２００４年１月）

Ｃ（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
	& WO 2001/072745 A1 & US 2002/0019404 A1 & EP 1274705 A1	
X	JP 8-503971 A（チバーガイギー　アクチェンゲゼルシャフト）1996.04.30 特許請求の範囲１、６、９～１１、第３１頁第１９行～第３７頁第１０行など & WO 95/09847 A1 & EP 672035 A1 & US 5612340 A	1, 2, 4–7
A	WO 2002/096905 A1 (Vertex Pharmaceuticals Incorporated) 2002.12.05. 請求の範囲１、７、１１、１３など & US2003/0119856 A1 & EP 1392684 A1	1–7
PX	WO 2004/043953 A1 (CYCLACEL LIMITED) 2004.05.27 請求の範囲、表１の化合物１、４５など、表２など & AU 2003/301977 A1	1–7
EX	WO 2005/052147 A2 (CYCLACEL LIMITED) 2005.06.09 請求の範囲１６、４５～５０など （ファミリーなし）	1–7